A Dissertation on

"A STUDY ON ESTIMATED GLOMERULAR FILTRATION RATE AS A PREDICTOR OF RENAL DYSFUNCTION AMONG ADULT HIV PATIENTS ON HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART)

Dissertation submitted to

THE TAMILNADU Dr.M.G.R. MEDICAL UNIVERSITY

CHENNAI – 600 032

With partial fulfillment of the regulations

For the award of the degree of

M.D. GENERAL MEDICINE

BRANCH – I

Department of General Medicine

Coimbatore Medical College Hospital

Coimbatore – 641 018

CERTIFICATE

This is to certify that the dissertation **"A STUDY ON ESTIMATED GLOMERULAR FILTRATION RATE (eGFR) AS A PREDICTOR OF RENAL DYSFUNCTION AMONG ADULT HIV PATIENTS ON HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART)",** is a bonafide research work done **by Dr.K.Gayathri**, Post graduate in **M.D. General Medicine** under my direct guidance and supervision to my satisfaction ,in partial fulfillment of the requirements for the degree of **M.D. General Medicine.**

Date : **Guide, Professor & Chief**
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DECLARATION

I solemnly declare that this dissertation titled **"A STUDY ON ESTIMATED GLOMERULAR FILTRATION RATE (eGFR) AS A PREDICTOR OF RENAL DYSFUNCTION AMONG ADULT HIV PATIENTS ON HAART (HIGHLY ACTIVE ANTIRETROVIRAL THERAPY)"** is a bonafide and genuine research work carried out by me from AUGUST 2013 to JUNE 2014 under the guidance and supervision of **Professor Dr.KUMAR NATARAJAN .M.D.,** Head of Department of Medicine , Coimbatore Medical College, Coimbatore.

This dissertation is submitted to The Tamilnadu Dr. M.G.R. Medical University towards the partial fulfillment of the requirement for the award of **MD Degree in General Medicine** (Branch I) .

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DATE : **Dr .K. GAYATHRI**

PLACE :

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ABBREVIATIONS

HIV	-	Human Immunodeficiency Virus
AIDS	-	Acquired Immuno Deficiency Virus
ART	-	Anti Retroviral Therapy
eGFR	-	Estimated Glomerular Filtration Rate
ESRD	-	End Stage Renal Disease
CKD	-	Chronic Kidney Disease
HBV	-	Hepatitis B virus
HCV	-	Hepatitis C virus
FSGS	-	Focal Segmental Glomerulosclerosis
HIVAN	-	HIV Associated Nephropathy
HIVMA / IDSA	-	HIV Medicine Association / Infectious Diseases Society of America
HAART	-	Highly Active Anti Retroviral Therapy
HIVICK	-	HIV Immune Complex Kidney disease
TTP	-	Thrombotic Thrombocytopenic Purpura
HUS	-	Hemolytic Uremia Syndrome
DART	-	Development of AntiRetroviral Therapy Trial in Africa
NKF	-	National Kidney Foundation
GN	-	Glomerulonephritis

TDF	-	Tenofovir
PI	-	Protease Inhibitor
NRTI	-	Nucleoside Reverse Transcriptase Inhibitors
NNRTI	-	Non Nucleoside Reverse Transcriptase Inhibitors
DEXA	-	Dual-energy X-ray absorptiometry
ELISA	-	Enzyme Linked Immunosorbent Assay
CDC	-	Center for Disease Control
EACS	-	European Aids Clinical Society Guidelines
NACO	-	National AIDS Control Organisation

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ABSTRACT

INTRODUCTION: Renal dysfunction is the common complication of HIV infection with a prevalence of 30 % in HIV patients. The spectrum of renal dysfunction is multifactorial ranging from exacerbation of chronic kidney disease to acute kidney injury. Kidney disease in the setting of HIV can pose a significant challenge to patients and clinicians by increasing the risk for AIDS-defining illness, hospitalization, and death.

OBJECTIVES: The prevalence of renal dysfunction among HIV-1 infected outpatients starting ART in India is limited. Recent recommendations to include the Nephrotoxic drug Tenofovir in first-line ART regimens make clarification of this issue urgent

METHODOLOGY : We screened for renal dysfunction by measuring serum Creatinine, urea, Microalbuminuria, USG – KUB, low CD4 counts and Opportunistic infections in HIV-positive patients initiating ART at Coimbatore Medical College Hospital . We excluded patients with preexisting renal disease, hypertension, diabetes, pregnancy or Hepatitis B/ C virus co-infection. eGFR were calculated by Cockcroft-Gault Equation, and eGFR was categorized accordingly based on National Kidney Foundation staging of Chronic Kidney disease : < 60 ml/min/1.73 m^2 (Grade 3 or less) ; 60- 90 ml/min/1.73 m^2 (Grade 2); <90 ml/min/1.73m^2 (

grade 1 or normal). e GFR calculated at the end of study was compared with Age, Gender, weight, CD4 counts , Urea , Creatinine and with different types of ART regimen used by the study population.

RESULTS: Only 21 (21%) of 100 enrolled patients had normal eGFRs (Grade 0 or 1) above 90ml/min/1.73m2. Grade 2 renal dysfunction (eGFR between 60 and 90 ml/min/1.73m2) was present in 37 patients (37%), and 42 patients (42%) had Grade 3 dysfunction 0r less (eGFR < 60 ml/min 1.73m2). Microalbuminuria was detected in 47% of patients. Mean eGFR was 69.28. 70% of patients fall under Tenofovir based regimen. Of which 64 % patients falls in eGFR <90 ml/min and in particular 38% falls under eGFR < 60 ml/min which indicates moderate to severe renal dysfunction. Majority of them in WHO clinical stage I and low CD4 count <200 associated with decline in eGFR.

CONCLUSION : Renal dysfunction was highly prevalent in this population of HIV-positive outpatients initiating first ART in Coimbatore Medical College Hospital , Coimbatore. This highlights the critical and underappreciated need to monitor renal function in HIV-positive patients, particularly given the increasing use of tenofovir in first-line ART.

Key words : eGFR: estimated glomerular filtration rate, ART : Antiretroviral Therapy , Renal dysfunction.

INTRODUCTION

Renal dysfunction is the common complication of HIV infection with a prevalence of 30% in HIV infected patients. The spectrum of kidney dysfunction is broad, ranging from exacerbation of common kidney diseases to acute and chronic conditions.[1] The causes of renal dysfunction are multifactorial which includes HIV infection per se, opportunistic infections , co-morbidities, and anti retroviral therapy . AIDS-related kidney disease, especially HIVAN (HIV associated Nephropathy) has become a relatively common cause of end-stage renal disease (ESRD) requiring renal replacement therapy and may be associated with progression to AIDS and death. [2]

Elevated serum creatinine is the first evidence of renal dysfunction. Increase in Serum creatinine from baseline should prompt an evaluation. The estimated Glomerular filtration rate (eGFR) is a direct measure of kidney function and reduces before the onset of symptoms of Renal failure. Severity of kidney disease directly correlates with decrease in GFR which can be calculated in the clinical setting using one of the three most commonly used equations:

1. Cockcroft – Gault (CG) formula

2. Modification of Diet in Renal Disease formula (MDRD)

3. Chronic Kidney Disease Epidemiology Consortium formula (CKD-EPI)

Any of these equations may be used to follow trends in creatinine ,as part of determining GFR. Cockcroft-Gault equation is the most commonly used which estimates GFR using serum creatinine measurements and anthropometric variables.

The incidence and spectrum of kidney diseases in HIV have been dramatically altered by ART .The risk for ESRD has been reduced and survival on dialysis is expected to improve with newer antiretroviral drug therapies .

Patients with HIVAN who are on effective ART have a slower decrease in GFR and less incidents of fulminant renal failure .HAART is responsible for at least a 30% reduction in new ESRD cases from HIVAN[3] .However, initiation of ART may not have a beneficial effect on the natural history of other forms of CKD, such as IgA nephropathy and diabetes, which could be mistaken for HIVAN when a biopsy is not obtained.

The present study was undertaken with an aim to investigate the factors associated with decline in estimated GFR using CG formula among the patients initiated on Highly Active AntiRetroviral Therapy (HAART) and its correlation with renal dysfunction and progression to end stage renal failure.

OBJECTIVES

1. To study the Renal Changes in Adult HIV Patients following first line HAART initiation using estimated Glomerular filtration rate (eGFR).

2. To study the Renal changes and decline in eGFR with respect to the different HAART regimens after the HAART initiation by using Cockcroft – Gault formula.

3. To consider that close monitoring of Renal function is important ,as the current use of specific antiretrovirals may result in an increased risk of eGFR decline in HIV – 1 infected patients on HAART.

REVIEW OF LITERATURE

HISTORY OF THE HIV /AIDS

Acquired Immunodeficiency Syndrome (AIDS) is a global epidemic caused by Human Immunodeficiency Virus (HIV) currently sweeping throughout the world.

1981 – New syndrome AIDS was first recognized in the intial outbreak with high mortalility, when US , CDC reported high number of cases of rare cancer , Kaposi sarcoma and rare Pneumocystitis jiroveci pneumoni among healthy homosexual men

1983 – HIV was isolated from a patient with lymphadenopathy by

Dr.Luc Montagnier

1985 – Cases of AIDS reported in 55 countries

FDA approved ELISA as sensitive diagnostic test

1987 – WHO estimated upto 1,50,000 cases exist worldwide

Azidothymidine became first anti – HIV drug approved by FDA

1988 – World AIDS day was first declared by WHO on December 1

1990 – WHO estimates nearly 9 million people with HIV and 1 million with AIDS

1991 - First protease inhibitor , Saquinavir approved by FDA

2000 – UNAIDS estimates 53 million people worldwide have contracted HIV/AIDS and 17 million died so far

2006 – June 5 marks a quarterly century since first AIDS case reported[4].

ORIGIN OF HIV/AIDS

In early 1980's one hypothesis was put forward that , there exits a close genetic relationship between humans and primates and the HIV virus was transmitted to humans from primates .Non human primates (monkeys and apes) are only an asymptomatic carrier of HIV like virus called SIVs (Simian Immunodeficiency Virus) and no disease manifests in these primates.

Genetic sequences of HIV and SIV were compared. .In 1989,

scientist demonstrated that RNA sequence of SIV from both captive and wild Sooty mangabeys were similar to HIV – 2[5].This supports the

overlapping geographical distribution and idea of cross species transmission in West Africa. The origin of this HIV -1 virus was unclear for many years.

The natural habitat of Chimpanzee and Gorilla coincides with geography of HIV -1 epidemics in central Africa and their SIV and human HIV -1 sequences were similar[6]. Most likely the virus was acquired through killing and butchering chimps and monkeys in the "bushmeat" trade.

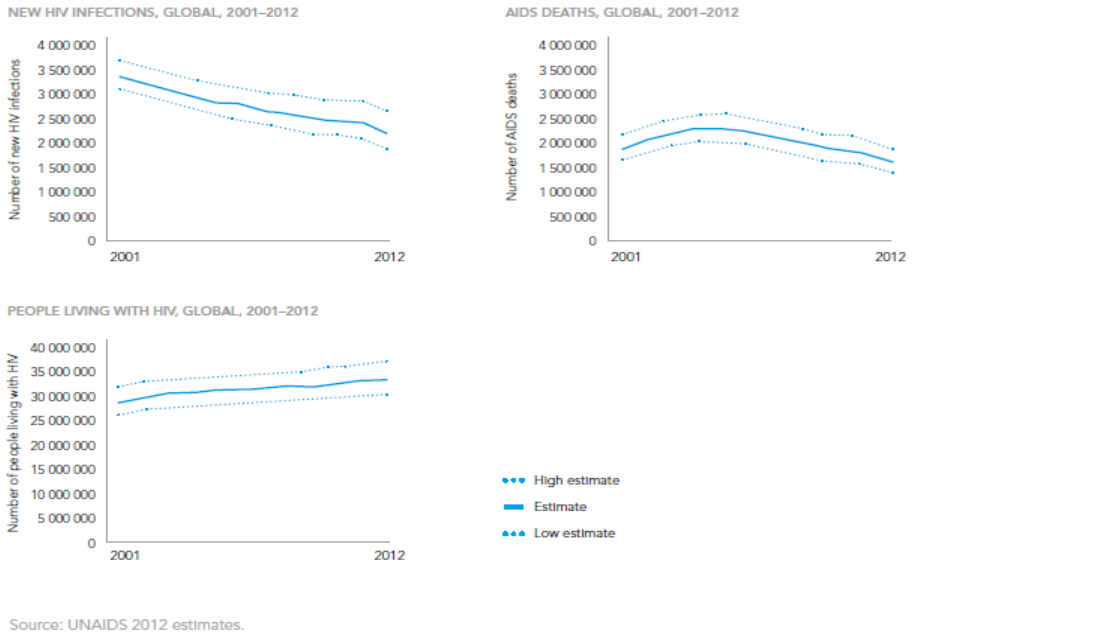
Two types of HIV can infect humans HIV- 1 and HIV- 2.HIV -1 is most common and more widespread throughout the world . HIV – 1 has several subtypes (M,N,O,P) and has different geographic distributions. AIDS pandemic s primarily caused by HIV -1 M group. HIV 2 mostly occurs in West Africa. It has subtypes from A through G.

EPIDEOMOLOGY

Globally, an estimated 35.3 (32.2–38.8) million people were living with HIV in 2012. An increase from previous years as more people are receiving the life-saving antiretroviral therapy.

There were 2.3 (1.9–2.7) million new HIV infections globally, showing a 33% decline in the number of new infections from 3.4 (3.1–3.7) million in 2001. At the same time the number of AIDS deaths is also declining with 1.6 (1.4–1.9) million AIDS deaths in 2012, down from 2.3 (2.1–2.6) million in 2005 [7.] **Graph 1 .**

Numbers of people living with HIV, new HIV infections, and AIDS deaths, 2001-2012, globally



Source: UNAIDS 2012 estimates.

STRUCTURE OF HIV VIRUS

The integrated form of HIV – 1 ,also known as provirus is approximately 9.8 kilobases in length .The genes are located in the central region of proviral DNA and encodes atleast 9 proteins. The median incubation period is ten years [8.] **Figure 1 .**

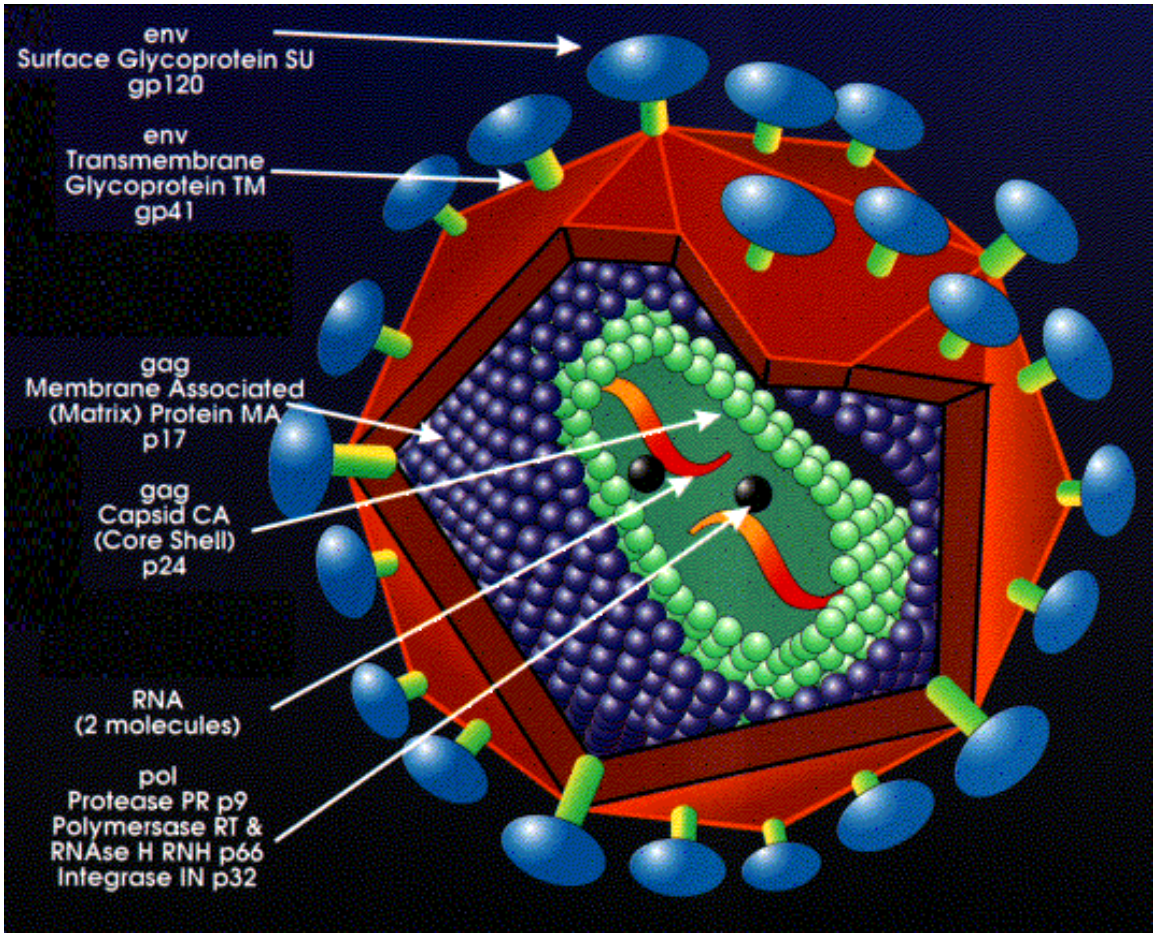
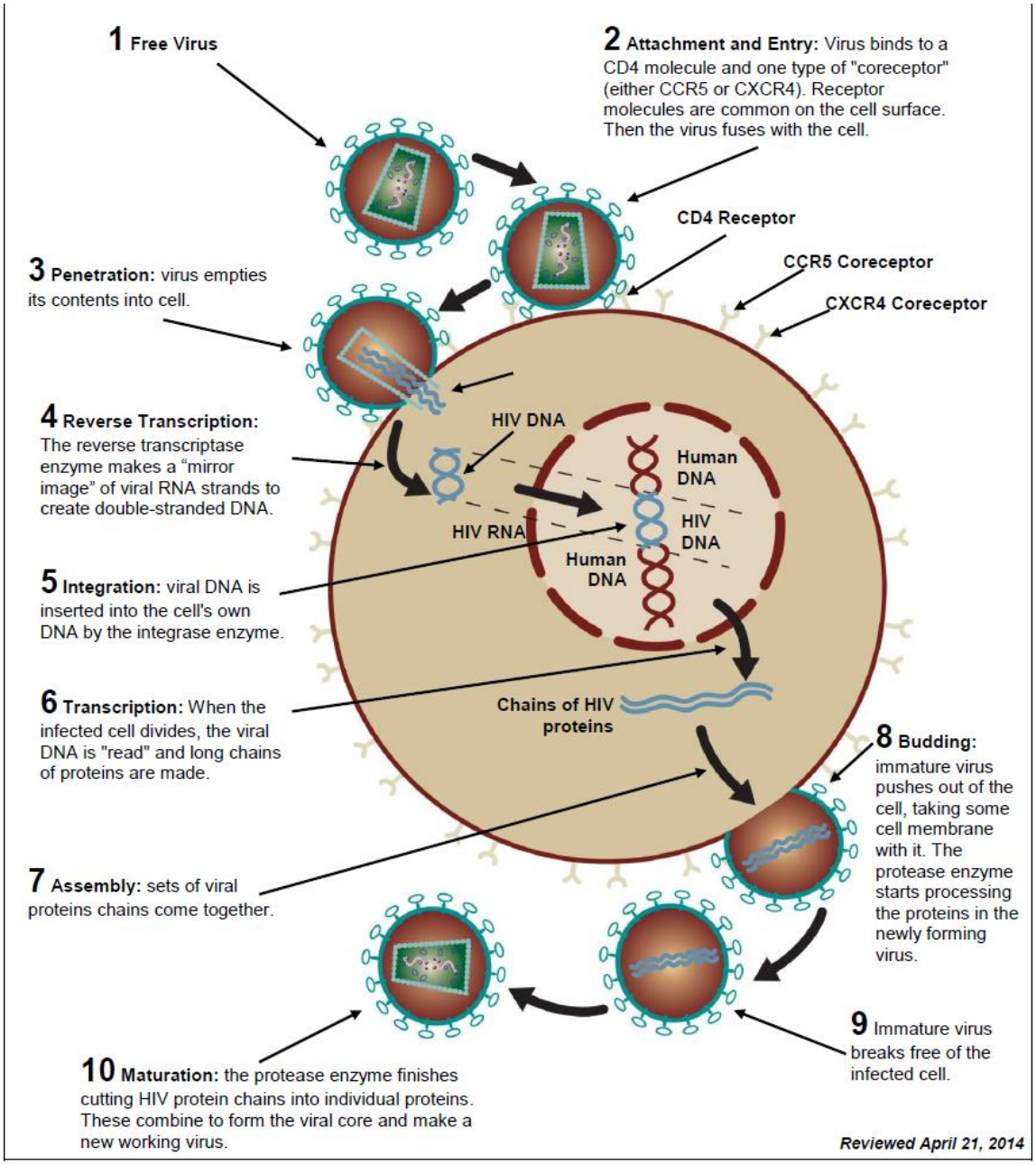


Figure 2 : HIV LIFE CYCLE



1993 Revised Classification System for HIV Infection

The revised CDC classification system for HIV-infected adolescents and adults categorizes persons on the basis of clinical conditions associated with HIV infection and CD4+ T- lymphocyte counts. The system is based on three ranges of CD4+ T- lymphocyte counts and three clinical categories and is represented by a matrix of nine mutually exclusive categories

CD4+ T-Lymphocyte Categories

The three CD4+ T-lymphocyte categories are defined as follows:

Category 1: greater than or equal to 500 cells/mL

Category 2: 200-499 cells/uL

Category 3: less than 200 cells/uL

These categories correspond to CD4+ T-lymphocyte counts per microliter of blood and guide clinical and therapeutic actions in the management of HIV-infected adolescents and adults [9.]

CLINICAL CATEGORIES

Category A

Documented HIV infection in adults more than 13 years with persistent generalized lymphadenopathy , asymptomatic HIV infection, acute HIV infection with accompanying illness[10].Conditions in B and C have not occurred.

Category B

Symptomatic conditions in an HIV-infected adolescent or adult that are not included among conditions listed in clinical Category C and that meet at least one of the following criteria: a) the conditions are attributed to HIV infection or are indicative of a defect in cell-mediated immunity; or b) the conditions are considered by physicians to have a clinical course or to require management that is complicated by HIV infection.

Category C

Clinical conditions listed in the AIDS surveillance case definition. For classification purposes, once a Category C condition has occurred, the person will remain in Category C

Table 1 : 1993 Revised Classification System

CD4+ T cell Categories	A Asymtomatic, Acute HIV or PGL	B Symptomatic Not A or C	C AIDS- indicator Conditions
>500/micL	A_1	B_1	C_1
200-499/micL	A_2	B_2	C_2
< 200/micL	A_3	B_3	C_3

A_3 , B_3 ,C_1 ,C_2 ,C_3 category persons have AIDS according to 1993 surveillance case definition

CLINICAL ASSESSMENT BEFORE STARTING ART

After confirmation of HIV infection by serological or virological evidence , Clinical staging is used . Clinical staging in established HIV infection is given in Table 2 . It is useful for assessment at baseline before starting ART and to guide in making decision about starting ART and other prophylaxis [11,12.]

Table 2 : WHO CLINICAL STAGING OF ESTABLISHED HIV INFECTION [20]

HIV-associated symptoms	WHO clinical stage
Asymptomatic	1
Mild symptoms	2
Advanced symptoms	3
Severe symptoms	4

CLINICICAL ASSESSMENT OF PEOPLE RECEIVING ART:

Clinical status can be effectively reversed by different ART regimens with good viral suppression and immunological recovery .[13,14].People on ART for more than 24 weeks can have new or recurrent clinical staging events,which help in further decision making .In first 24 weeks its due to immune reconstitution. After 24 weeks its due to immune suppression [15,16.]

IMMUNOLOGICAL ASSESSEMENT BY CD4 COUNTS

The prime target cell for HIV virus is CD4+ T lymphocyte, as virus has high affinity for CD4 surface marker.[17]. Normal absolute lymphocyte count in adults, ranges from 500 to 1500 cells/mm3. As HIV disease advances , CD4 count progressively decreases and the risk and severity of opportunistic infection increases.

In response to effective combination ART ,CD4 counts increases though it takes many months [18]. Adults started on ART with CD4 counts >200-350 mm3 have better virological outcomes when compared to CD4 count <50mm3[13,14,19].

Commencing ART can be delayed if there is mild immunodeficiency (CD4 count >350mm3 in adults) or the patient is asymptomatic. So, CD4 testing is a useful guide in starting first line ART , initiating cotrimoxazole prophylaxsis , identifying treatment failure and to assess and monitor response to ART.

Table 3 : WHO IMMUNOLOGICAL STAGING OF ESTABLISHED HIV INFECTION [20]

HIV-associated immunodeficiency	Age-related CD4 values			
	<11 months (%CD4+)	12–35 months (%CD4+)	36–59 months (%CD4+)	>5 years (absolute number per mm³ or %CD4+)
None or not significant	>35	>30	>25	> 500
Mild	30–35	25–30	20–25	350–499
Advanced	25–29	20–24	15–19	200–349
Severe	<25	<20	<15	<200 *or* <15%

Table 4 : WHO CLINICAL STAGING IN ADULT HIV/AIDS WITH ESTABLISHED HIV INFECTION [20]

Clinical stage 1
Asymptomatic Persistent generalized lymphadenopathy
Clinical stage 2
Moderate unexplained weight loss (<10% of presumed or measured body weight)[I] Recurrent respiratory tract infections sinusitis, tonsillitis, otitis media and pharyngitis) Herpes zoster Angular cheilitis Recurrent oral ulceration Papular pruritic eruptions Seborrhoeic dermatitis Fungal nail infections

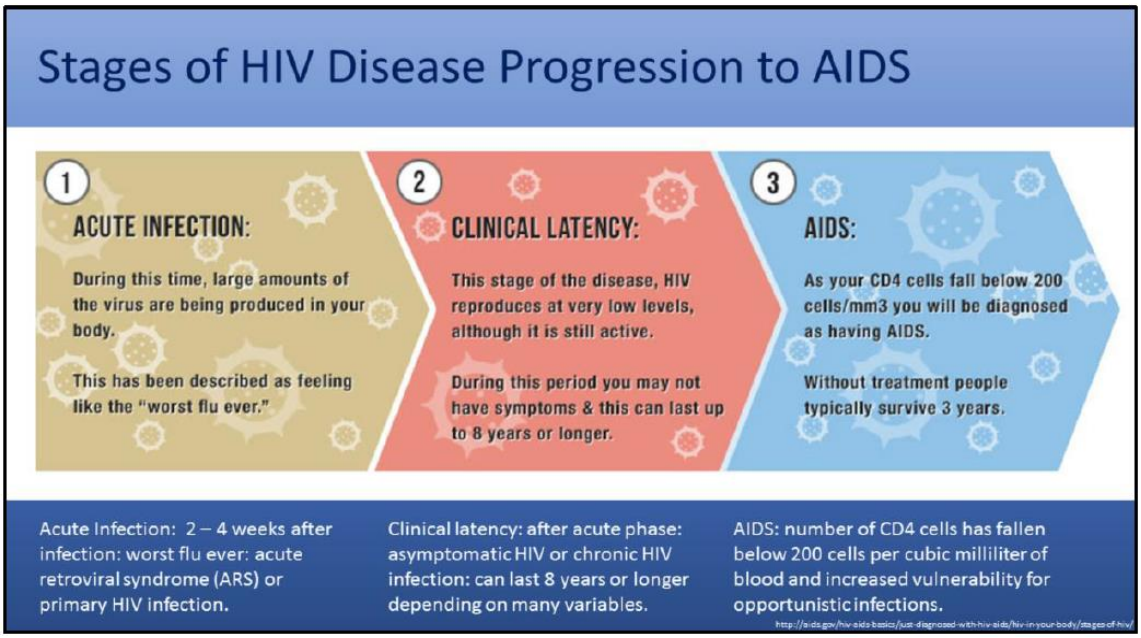
Clinical stage 3
Unexplained[i] severe weight loss (>10% of presumed or measured body weight)
Unexplained chronic diarrhoea for longer than one month
Unexplained persistent fever (above 37.6°C intermittent or constant, for longer than one month)
Persistent oral candidiasis
Oral hairy leukoplakia
Pulmonary tuberculosis (current)
Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis or bacteraemia)
Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 × 10^9 per litre) or chronic thrombocytopaenia (<50 × 10^9 per litre)
Clinical stage 4[ii]
HIV wasting syndrome
Pneumocystis pneumonia
Recurrent severe bacterial pneumonia
Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration or visceral at any site)
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Extrapulmonary tuberculosis
Kaposi's sarcoma
Cytomegalovirus infection (retinitis or infection of other organs)
Central nervous system toxoplasmosis
HIV encephalopathy
Extrapulmonary cryptococcosis including meningitis
Disseminated non-tuberculous mycobacterial infection
Progressive multifocal leukoencephalopathy
Chronic cryptosporidiosis (with diarrhoed)
Chronic isosporiasis
Disseminated mycosis (coccidiomycosis or histoplasmosis)
Recurrent non-typhoidal Salmonella bacteraemia
Lymphoma (cerebral or B-cell non-Hodgkin) or other solid HIV-associated tumours
Invasive cervical carcinoma
Atypical disseminated leishmaniasis
Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy

i Unexplained refers to where the condition is not explained by other causes.

ii Some additional specific conditions can also be included in regional classifications (such as reactivation of American trypanosomiasis [meningoencephalitis and/or myocarditis]) in the WHO Region of the Americas and disseminated penicilliosis in Asia).

COURSE OF UNTREATED HIV DISEASE:

Figure 3 :



Natural History of HIV Infection

- Viral transmission
- Primary HIV infection
- Seroconversion
- Asymptomatic HIV infection
- Symptomatic HIV infection
- AIDS

The first three constitute the window period.

VIRAL TRANSMISSION

HIV infects initially with tansmission of virus. The mean incubation period is 5 days .Within that people become infectious to others, even before the onset of any symptoms and life long they will remain infectious to others.

PRIMARY HIV INFECTION

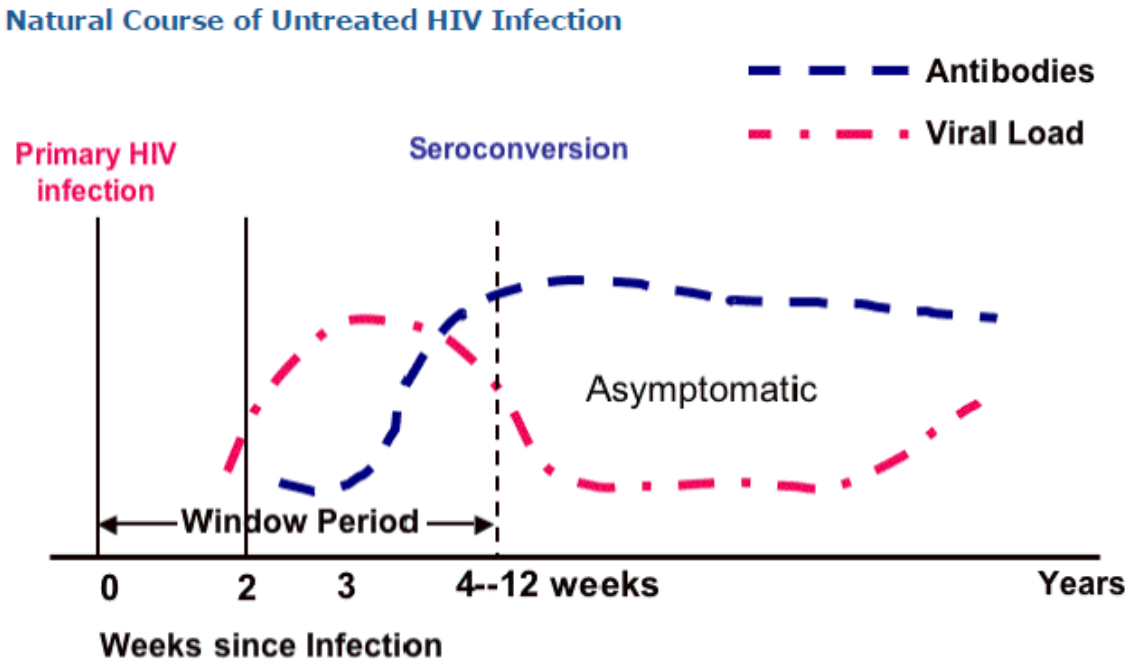
The virus initially localize to regional lymph nodes, after transmission and then disseminates to GIT ,genital tract and other lymphoid organs.[21] So in the first few weeks there is one million copies /mL of plasma viral load. [21] . In the following next few weeks ,plasma viremia decreases with effective cellular immune mechanism of host. [22}

Up to 70% of newly infected people experience "flu-like" symptoms (fevers, chills, night sweats, rashes). Within 14 days, Acute primary illness resolves spontaneously [23]

WINDOW PERIOD AND SEROCONVERSION

The window period begins with initial infection and continues until the virus can be detected by an HIV antibody test. Seroconversion is

the is the term for the point at which HIV antibodies are detectable and the window period ends. [23] See below, **Graph 2**



The first two weeks following infection are highly contagious but not detectable by HIV tests. Antibodies may begin to appear after 2 weeks but take up to 12 weeks or longer to reach seroconversion (eg, be detectable by current testing). As is seen on the line curves, the viral load continues to increase until there are sufficient antibodies to suppress, but not kill, the virus. Once the antibodies become active, an untreated patient may be asymptomatic for 10 years before the antibodies are no longer able to suppress the virus and the person becomes symptomatic. Source: Adapted from Conway & Bartlett, 2003.

ASYMTOMATIC HIV INFECTION (CLINICAL LATENCY PERIOD)

Following seroconversion patient enters a prolonged asymptomatic period. The person may look and feel healthy , but still virological and immunological progression occurs, which can go for longer than 10 years [23,24] During this time the only indication of clinical HIV infection occurs through testing or the presence of swollen lymph glands .

SYMTOMATIC HIV INFECTION

Symptomatic HIV disease is due to Progressive and sub-clinical, immune deterioration of the host defenses . It can take 5 to 7 years for mild symptoms to occur. Some common symptoms,which are non is specific to HIV disease are[23]:

- Persistent low grade fever
- Persistent diarrhea
- Significant weight loss
- Chronic vaginal or oral thrush
- Recurring herpes blisters

LATE STAGE AIDS

Late stage AIDS disease is diagnosed by HIV specific blood test and patients general condition. In late stages, the T-cell count drops down to 200 or less, and opportunistic infections develop. These are infections and illnesses that the normal immune system can suppress or present. There is an increase in Plasma viral load few years before the development of AIDS **[25,26]**

Death occurs from extensive involvement of vital organs , from effects of circulatory toxins, circulatory and haematopoietic failure .

RENAL DISEASE AND HIV

HISTORICAL PERSPECTIVE

In 1984, Roa and others diagnosed a focal and segmental glomerulosclerosis in 10 out of 92 black patients diagnosed to have AIDS at King Country Medical center,New York city, and there was a rapid progression to severe uremia in all those patients [27]. This report supported HIV as the causative agent for AIDS.

In certain geographical areas existence of AIDS nephropathy , was not accepted due to low incidence . Since then ,the prevalence of HIVAN has increased over past 25 years , attained peak in mid 1990's and then remained stable after introduction of ART with an initial decline since 1996[28} .

SPECTRUM AND EPIDEOMOLOGY

Kidneys have been reported to be commonly involved in HIV infection with a prevalence of 30%. It is a proven reservoir of HIV infection. The spectrum of kidney involvement is broad ranging from exacerbation of common kidney diseases , fluid and electrolyte imbalances to HIVAN which progress rapidly to renal failure **[1].**

Acute renal failure is more prevalent in HIV positive individuals. The common causes include prerenal azotemia following poor fluid intake, diarrhoea and hypovolemia. ATN can be due effects of Nephrotoxic drugs and sepsis [33].Volume depletion in HIV patients is an important predisposing factor for Acute renal failure.

Prevalence of HIVAN is from 3% to 12% found in autopsy series,as data for HIVAN not exist in AIDS case definition [30]. However, because of the lack of definitive diagnosis of HIVAN by kidney biopsy, most studies provide estimates of renal involvement (eGFR) in HIV-1–infected individuals rather than true prevalence of HIVAN [29] . It causes progressive renal failure with both glomerular and tubulointerstitial components.

Chronic renal failure (CKD) can occur in HIV patients . The risk factors are same as in HIV negative persons. The evaluation should begin with ruling out the secondary causes of glomerular disease which manifest as proteinuria and elevated urea and creatinine like Diabetes, Hypertension, Malignancy, HCV, HBV or Syphilis.

Urine analysis is important as it is very sensitive indicator of renal dysfunction even with normal GFR, whereas GFR needs to drop to 50% of normal in order to reflect any abnormality in renal functions.

HIV associated renal diseases are due to HIV infection per se or due to certain antiretroviral drugs used or due to pharmocological drugs used in the treatment and prophylaxis of associated opportunistic infections.

Atleast transient alternations in renal function can occur in all stages of diseases in individuals with HIV infection. Mortality due to renal disease in HIV is correlated with complications of infections rather than due to presence of renal disease or need for dialysis per se [34,35]

In HIV positive patients, ART has modified the manifestations of renal diseases , especially the incidence of HIVAN , risk of ESRD and the need for hem dialysis has been reduced in HAART era [31]. Patients with HIVAN who are on ART will have atleast 30% reduction in fulminant renal failure [32]

GLOMERULAR FILTRATION RATE

The central function of the kidney is to filter the metabolic waste products from the blood and to eliminate them from the body. eGFR is widely used and is the best overall measure of renal function.

GFR indicates amount of filtrate passing into the Bowmann space from the glomerular capillaries per unit of time, and it is calculated by measuring the clearance of specific marker substance. GFR varies with sex and age, but is 120 - 130 ml/min/ 1.73 m2 surface area approximately in adults [38].

A substance or molecule which is an ideal marker for measuring the Clearance(CL) should not be protein bound, is freely filtered at the glomerulus , neither reabsorbed, secreted , metabolise or synthesized by the renal tubules and excreted only by the kidney. So far ,such an ideal biomarker is not found .

GFR can be measured as a renal clearance of various exogenous markers, which are of impractical in routine use. They are Inulin, Non-radiolabelled contrast media (iothalamate/iohexol) , Radiolabelled contrast media (51Cr-EDTA), 99mTc DPTA, I 131 Hippuran.

Endogenous markers include Urea, Creatinine and Cystatin C. The Commonly used marker to measure GFR in clinical laboratory is serum Creatinine , however it has multiple limitations.[37] Rather than depending on GFR alone, Plasma creatinine is also influenced by factors like muscular mass, diet, age and gender.

The new endogenous biomarkers are beta2-microgobulin and Cystatin C. Serum Cystatin C is a potential alternative to creatinine for estimating GFR. In view of prognosis , it's a better marker in chronic kidney disease than plasma creatinine.[36]

ESTIMATING GLOMERULAR FILTRATION RATE

For GFR estimation from plasma creatinine concentration, various formulas which incorporate variables like age, gender, height and weight can be used. Here are some commonly used formulas :

1. COCKCROFT-GAULT (CG) equation :

It was derived in 1976 from a cohort of 290 hospital patients.[39]. It is based on patient age ,gender , weight and serum creatinine.

CG equation:

$$\text{e GFR (ml/min)} = \frac{(140\text{-age in years}) \times \text{Weight in Kg}}{(\text{Weight}/72) \times \text{Serum creatinine (mg/dL)}}$$

(In female , multiply the result by 0.85)

The above formula is adjusted for black patients, also it may overestimate creatinine clearance in patients who are malnourished or who have edema. This equation was validated in 200 hospitals with a broad range of creatinine clearance values [39].

2. THE MODIFICATION OF DIET IN RENAL DISEASE (MDRD) Formula :

It was derived in 1999 from a cohort of 1628 cases with CKD in the MDRD study[40]. It Estimates GFR based on age, sex , race , and serum creatinine.

MDRD Formula:

$$GFR = 186 \times (SCr)^{-1.154} \times (Age)^{-0.203}$$
$$\times 0.742 \text{ (if patient is female)} \times 1.212 \text{ (if patient is black)}$$

The MDRD formula was validated in a sample of patients in MDRD study, who also had CKD and GFR values between 20-60 ml/min/1.73 $m^{2.}$ CG equation measures creatinine clearance(CL) , while MDRD measure GFR directly.

3. THE CHRONIC KIDNEY DISEASE EPIDEOMOLOGY COLLOBORATION (CKD-EPI) Formula :

It was derived in 2009 from a collaboration of clinical studies and data from the Nutrition Examination Survey and National health in America between 1999 and 2006 [41]. It is based on age, race and serum creatinine.

CKD-EPI Formula :

$$GFR = 141 \times min(Scr/\kappa, 1)^{\alpha} \times max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018\,[if\,female] \times 1.159\,[if\,black]$$

where SCr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

The CKD-EPI formula was found to be more specific than the MDRD study formula especially at high glomerular filtration rates in the validation sample.

Cockgroft and Gault (CG) equation is the best validated and widely employed equation.

ACUTE KIDNEY INJURY

Definition

The AIDS Clinical Trial group has defined Acute Kidney Injury (AKI) in HIV-seropositive patients as a creatinine level more than 1.5 mg/dl or a 1.3 fold raise from baseline that can be reversible within 3 months .

The basic causes and mechanisms of ARF is similar to as in HIV negative patients. But some causes of AKI are specific to HIV infection. . It may be classified as prerenal, intrinsic and post renal causes.

In hospitalized patient , the most common causes are pre renal causes in 38% of patients due to volume depletion and Acute Tubular

Necrosis (ATN) in 58% of patients , contributing 52% in overall ,due to infection, septicemia, ischemia, bleeding, hypoalbuminaemia, or nephrotoxins[42]. Interstitial nephritis , obstructive nephropathy and interstitial nephritis are very rare causes.

There is an increasing incidence of HIV – associated thrombotic microangiopathies and rhabdomyolysis, the latter due to the use of statins with antiretroviral drugs.

Post-renal AKI ,though rare , can occur due to malignancy , lymph nodes, retroperitoneal fibrosis, or crystalluria due to indinavir, foscarnet, sulphadiazine or acyclovir. More recently, atazanavir has been associated with nephrolithiasis, but unlike indinavir[43] this protease inhibitor has not been associated with obstructive AKI or with AIN.

Table 5: Causes of Acute Kidney Injury in HIV- infected individuals[43]

Pre-renal Causes
Hypovolemia: diarrhea, nausea/ vomiting, decreased oral intake
Effective Hypovolemia: hypotension, sepsis, liver disease, hypoalbuminemia (nephrotic syndrome, proteinuria, malnutrition)
Intrinsic Renal Injury
Acute tubular necrosis
Ischemic: hypovolemia, shock, sepsis, cardiopulmonary compromise
Nephrotoxic: medications, radiocontrast
Rhabomyolysis
Parenchymal infection (mycobacterial, fungal, viral)
Interstitial nephritis
Hemolytic uremic syndrome
Glomerular disease: HIVAN, glomerulonephritis
Post-renal Causes
Intra-renal tubular obstruction: crystalluria from medications, tumor lysis syndrome
Ureter or bladder obstruction: nephrolithiasis, lymphadenopathy/ tumor, fungus ball, blood clots, neurogenic bladder

Table 6 : RISK factors for HIV induced AKI [43]

Older age
Diabetes mellitus
Chronic kidney disease
Liver disease/ Hepatitis C
Low CD4 count
High HIV RNA
History of AIDS-defining illness
History of antiretroviral exposure

AKI and Oppurtunistic Infections (OI's)

In Pre-HAART era, AKI incidence and mortality was due to septicemia and opportunistic infections.In ART era, the incidence due to opportunistic infections are rare, which are :

1. Parenchymal fungal infections

2. Granulomatous nephritis with Mycobacterium

3. Interstitial nephritis due to Epstein Barr Virus, Polyoma virus and Cytomegalovirus.

PNEUMOCYSTITIS PNEUMONIA

AKI in pnemocystitis is due to clumps of organisms obstructing tubular and glomerular capillaries, which leads to form renal calcification on Computerised Tomogarphy [44].

Cotrimoxazole in high dose is a nephrotoxic agent and it is use should be used carefully. In patients with renal impairment , the treatment is as follows given in Table

Table 7 : PCP treatment in renal insufficiency

	GFR normal	GFR >50 ml/min	GFR 10-50 ml/min	GFR <10 ml/min	Dose adaptation for HD/CAPD/cont. NET
Cotrimoxazole	960 mg 3 x 3/die (total of 120 mg/ kg daily)	960 mg 2 x 3/die (100 % every 12 h)	960 mg 1-2 x 3/die (100 % every 12-24 h)	480 mg 1 x 3/die (50 % every 24 h)	HD: + half dose after dialysis CAPD: no adaptation CAVH: GFR 10-50 CVVHD: GFR < 10
Dapsone	100 mg every 24 h	50-100 %	50 %	avoid	avoid
Atovaquone	750 mg every 12 h	100 %**	100 %**	100 %**	HD: no adaptation CAPD: no adaptation* CAVH: (GFR < 10)**
Pentamidine	4 mg/kg every 24 h	100 %	100 % every 24-36 h	100 % every 48 h see text !!!	HD: (GFR < 10)*** CAPD: (GFR < 10)** CAVH: (GFR < 10)**

* no studies available, normal dosage recommended,

** no studies available, dosage as for GFR < 10ml/min recommended.

(cont. NET = continuous dialysis, HD = intermittent hemodialysis, CAPD = continuous ambulant peritoneal dialysis; CAVH = continuous arterio-venous hemofiltration, CVVHD = continuous veno-veno hemodiafiltration).

CMV, HSV AND VZV infection

Table 8 : Treatment of CMV, HSV, VZV infection in renal insufficiency

Drug	GFR normal	GFR > 50 ml/min	GFR 10-50 ml/min	GFR < 10 ml/min	Dose adaptation for HD/CAPD/cont. NET
Acyclovir	5-10 mg/kg every 8 h	5 mg/kg every 8-12 h	5 mg/kg every 12-24 h	2.5 mg/kg every 24 h	HD: Dose after dialysis CAPD: GFR < 10 CAVH: 3.5 mg/kg every 24 h CVVHD: 6.5-15 mg/kg every 24 h
Ganciclovir	5 mg/kg every 12 h	3 mg/kg every 12 h if GFR 25-50 ml	3 mg/kg every 24 h if GFR 10-25 ml	15 mg/kg every 24 h	HD: Dose after dialysis CAPD: GFR < 10 CAVH: 3.5 mg/kg every 24 h CVVHD: 2.5 mg/kg every 24 h
Valgan-ciclovir	900 mg every 12 h	GFR 40-59 ml/min 450 mg every 12 h GFR 25-39 ml/min 450 mg every 24 h GFR 10-24 ml/min 450 mg every 48 h for induction		unknown	unknown
Foscavir	90 mg/kg every 12 h	50-100 %	10-50 %	avoid	HD: Dose after dialysis CAPD: 60 mg/kg every 48-72 h CAVH: GFR 10-50
Cidofovir	5 mg/kg every 7 days	100 %	0.5-2 mg/kg every 7 days	avoid	HD: GFR 10-50 CAPD: GFR 10-50 CAVH: avoid
Famciclovir	250 mg every 8 h p.o.	Every 12 h	Every 48 h	50 % every 48 h	HD: Dose after dialysis CAPD: ? CAVH: GFR 10-50

(cont. NET = continuous dialysis, HD = intermittent hemodialysis, CAPD = continuous ambulant peritoneal dialysis; CAVH = continuous arterio-venous hemofiltration, CVVHD = continuous veno-veno hemodiafiltration).

TOXOPLASMA ENCEPHALITIS

Table 9 : Treatment of cerebral toxoplasmosis in renal insufficiency

	GFR normal	GFR > 50 ml/min	GFR 10-50 ml/min	GFR < 10 ml /min	Dose adaptation for HD/CAPD/cont. NET
Pyrimethamine	50-75 mg every 24 h	100 %	100 %	100 %	HD: no adaptation CAPD: no adaptation CAVH: no adaptation
Clindamycin	150-300 mg every 6 h	100 %	100 %	100 %	HD: no adaptation CAPD: (GFR < 10)* CAVH: (GFR < 10)* CVVHD: GFR normal
Sulfadiazine	2 g every 6 h	Avoid	Avoid	Avoid	Avoid

*= no studies available, dosage as for GFR < 10 ml/min recommended.
(cont. NET = continuous dialysis, HD = intermittent hemodialysis, CAPD = continuous ambulant peritoneal dialysis; CAVH = continuous arterio-venous hemofiltration, CVVHD = continuous veno-veno hemodiafiltration).

In the post – HAART era

After the introduction of ART , cases of Acute Interstitial Nephritis (AIN) due to IRIS (Immune Reconstitution Inflammatory Syndrome) have been reported. IRIS is a systemic inflammatory response to infections or to non-infectious diseases that can manifest as the immune system is restored after the initiation of ART.[46]

It should be considered after excluding other causes of ARF. In these cases, renal function may drastically improve after initiation of steroid therapy. In one recent study reported from London , IRIS contributed to 6

out of 144 patients within 90 days of initiation of ART, mostly due to exacerbation of infections like Mycobacterium avium, Cryptococcosus, Pneumocystitis, hepatitis B.[45]

CHRONIC RENAL FAILURE

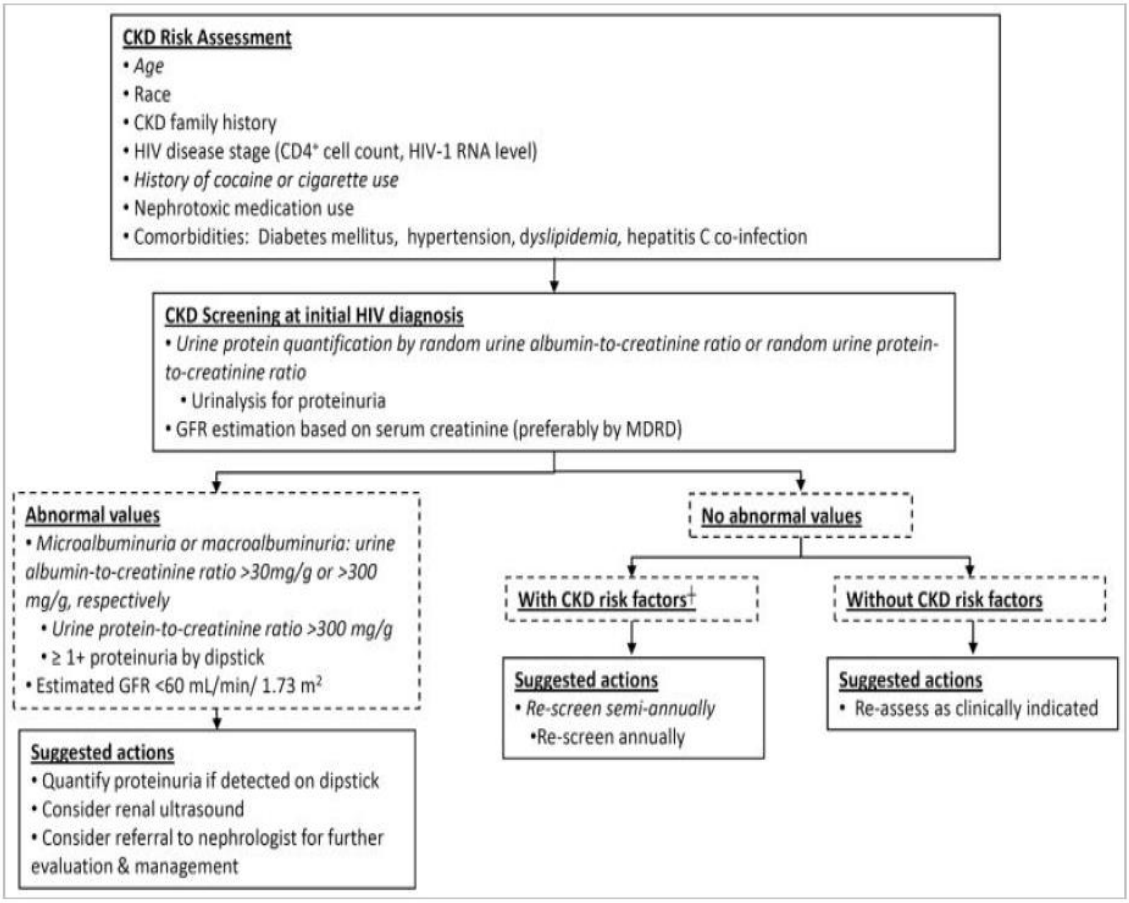
DEFINITION

National Kidney Foundation defines Chronic Kidney Disease by the presence of protenuria and estimated GFR < 60 mL/min/1.73m^2 of atleast 3 months duration. HIVMA –IDSA guidelines also recommends this definition. It graded by calculating the estimated glomerular filtration rate using modified Cockcroft-Gault equation or by use of the MDRD equation.[48]

The Table 10 gives guidelines for screening HIV patient for CKD.

This screening guidelines will helpful to follow up the patients who are started on ART with nephrotoxic potential, in particular Tenofovir. These patients may benefit from more frequent assessments of their GFR, serum phosphate levels, and urine albumin to monitor for early signs of nephrotoxicity.[47]

Table 10: NKF and IDSA guidelines for screening CKD



CKD risk factors: African American, $CD4^+$ cell count < 200 cells/mm^3, HIV-1 RNA >14,000 copies/ml , diabetes, hypertension, dyslipidemia, cocaine/cigarette use, hepatitis co-infection

.

Based on National Kidney Foundation(NKF) and Kidney Disease Outcome Quality Initiative (K/DOQI) Clinical Practice Guideliness ,CKD is classified into five stages, based on estimated GFR and irrespective of diagnosis given in **Table 11,**

STAGES OF CHRONIC KIDNEY DISEASE AND CLINICAL ACTION PLANS

Stage	Description	GFR (mL/min/1.73m²)	Action*
	At increased risk	≥90 (with CKD risk factors)	Screening CKD risk reduction
1.	Kidney damage with normal or ↑ GFR	≥90	Diagnosis and treatment Treatment of comorbid conditions, slowing progression, CVD risk reduction
2.	Kidney damage with mild ↓ GFR	60–89	Estimating progression
3.	Moderate ↓ GFR	30–59	Evaluating and treating complications
4.	Severe ↓ GFR	15–29	Preparation for kidney replacement therapy
5.	Kidney failure	<15 (or dialysis)	Replacement (if uremia present)

Even in post HAART era, there is increased mortality and progression to AIDS in Chronic kidney disease patients.[49]. Adverse effects with protease inhibitors (PIs) are more common in patients with CKD.[50]

There are various spectrum of hisopathology in HIV patients with CKD. Of the various causes of , the three variants are common,which include:

- Focal Segmental Glomerular sclerosis
- Immune complex renal disease
- Microangiopathic renal disease

HIVAN

HIV Associated Nephropathy (HIVAN) is the frequently recognized and most prevalent causes of CKD in HIV infected individuals. It is characteristically most common in African population when compared to Asian population and can occur in any CD4 count [51].

In virologically suppressed patients, HIVAN is extremely rare because here viral replication is directly related to renal injury. In untreated patients, HIV- associated nephropathy is typically characterized by abrupt decrease in renal function , asscociated with proteinuria of high grade, no pedal edema and large echogenic kidneys on ultrasound .

ART is found to preserve renal function and prolong survival in HIVAN. Therefore , even at the earliest sign of renal failure , ART initiation should be encouraged started in all individuals.

Clinical features

The onset is usually insidious. The patient may be asymptomatic and unaware of the renal dysfunction until the disease is advanced and only few renal function remains. It is generally a late manifestation years after HIV

infection. Very Rarely, HIVAN can present during acute HIV viral syndrome in primary infection

Late stages of HIVAN presents as nephrotic syndrome with :

- Nephrotic range proteinuria (> 3.5 gm/ 24 hours)
- Absence of Hypertension
- Peripheral edema may be present at times
- Less hyperlipidemia
- Hypoalbuminemia
- Rapid decline in GFR and progress to ESRD with
- Serum creatinine > 2mg/dL
- Large echogenic kidneys despite renal failure on ultrasound
- Renal biopsy shows findings of Focal Segmental Glomerulosclerosis (FSGS)

In Urinalysis ,there will be sediments with varying numbers of red blood cells , proteinaceous casts and epithelial cells of tubular origin. 25 % can have pyuria . Proteinuria may show a wide variation in values in patients with HIVAN.[52] .In one review of South African case reports , the mean value of proteinuria in biopsy specimens of HIVAN patients was 11.8 gm/d. , but the actual the range observed in the study was 0.7 to 40 gm/d.[52]

Histopathology

Definite diagniosis of HIVAN requires renal biopsy and it should be done if the clinical criteria meets without any contraindication. The decision for biopsy is controversial. Biopsy diagnosis is predictive only in 55- 60% of patients with HIVAN, even with classical clinical features.

To differrentiate HIVAN from other common forms of renal disease. (eg., immunoglobulin-A nephropathy, immune complex glomerulonephritis) ,there is a practice of doing renal biopsy in all HIV positive patients , whose daily protein excretion is more than 1 g /day [53].

In light microscopy ,the most common histological picture is Collapsing glomerulosclerosis and severe tubulointerstitial injury[54] .The capillary tuft of glomerulus is collapsed and may be sclerosed globally or segmentally . The unique feature is severe retraction of glomerular capillaries with podocyte swelling and hyperplasia which obliterates Bownmann's space as " pseudocresents" [55] shown in Fig 4 .

Tubulointerstitial disease is also a predominant feature with microcyst formation ,cylindrically dilated tubules containing large proteinaceous casts.

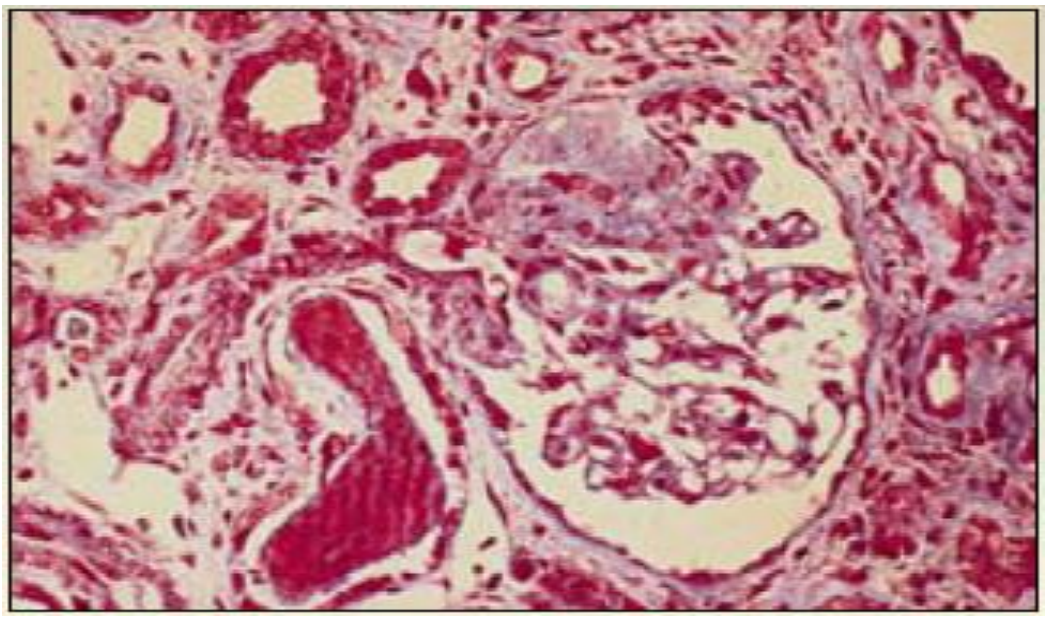


Fig 4:Trichrome staining in light microscopy shows a collapse of the glomerular tuft with sclerosis (bluish staining) of segment of glomerulus and interstitium . Dilated renal tubules are filled with proteinaceous material.

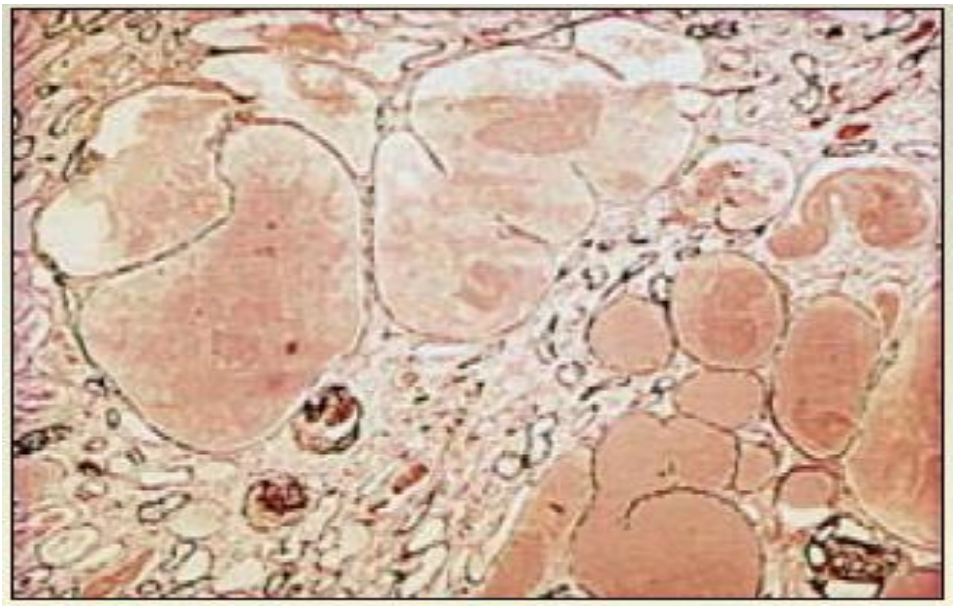


Fig 5 : Light microscopy picture showing microscopic dilatation of renal tubules enclosed with proteinaceous material.

In Immunofluorescent microscopy , staining for immunoglobulin G ,M , C3 in epithelial cells and A in sclerotic areas. In pododcytes, there is increase of proliferation markers of podocytes and decrease of differentiation markers [56].

Electron microscopy shows basement membrane wrinkling , proliferation of epithelial cell and effacements of foot process. In endothelial cells of glomerulus , presence of tubuloreticular structures is highly predictive of HIVAN.

Fig 6 : Electron microscopy showing a endothelial cell swelling in glomerulus with effacement of podocytes (black arrow) and tubulointerstitial inclusions (red arrow).

In HIVAN , though collaping glomerulopathy is the most common presenting lesion ,but other glomerular lesions like IgA nephropathy, cryoglobulimemia, amyloidosis , and lupus like immune glomerulopathy.

HIVAN causes rapid progression to renal failure and in turn to ESRD in pre antiretroviral era. HAART has made a dramatic change in the natural course of disease and has reported stabilization and improvement in disease including histological changes ,thus emphasis the importance of early prompt evaluation ,diagnosis and treatment[27] .

Current guidance is for initiation of HAART in all patients where HIVAN is confirmed irrespective of CD4 counts[57].

CAUSES OF CKD OTHER THAN HIVAN

Among non- HIVAN causes of glomerulopathies the most common are membranoproliferative glomerulonephritis, membranous nephropathy , HIV immune complex disease and diabetic nephropathy[49]. These disease attribute to CKD most commonly in non-black people, Hepatitis B coinfected ,and in people normal Blood Pressure and with high CD4 counts[49].

Based on biopsy findings, there is wide spectrum of glomerulonephritis , which is categorized as follows:

1.HIV – FSGS (‘classic disease ‘)

2.HIVICK : group includes Hepatitis B and Hepatitis C co-infection

The patterns in this group are:

- Mesangial proliferative
- Membranoproliferative (type I and III) ,lupus like nephritis
- Exudative – cresentric and proliferative Ig A
- Membranous

3.Various other glomerulopathies : This is big group with varied etiologies.

- Immunoactoid
- Minimal change
- Amyloidosis
- Nephrosclerosis and Comorbid disease – Diabetes, Hypertensive

4.HIV- TTP/HUS

Table 12 : IMMUNE COMPLEX KIDNEY DISEASE IN HIV[57]

HISTOLOGICAL PATTERN	IMPORTANT ECONDARY CAUSES/ASSOCITIONS IN HIV
HIV immune complex kidney disease (HIVICK)	
Membranous GN	Syphillis , HBV , Neoplasia
IgA Nephropathy	Chronic liver disease
Post infectious GN	Streptoccocal ,Staphylococcus infection. Bacterial, fungal, viral or parasitic disease
Mesangiocapillary GN	HCV, HBV, Chronic infection (eg.SBE), SLE, Drugs
Immunoactoid / Fibrillary GN	HCV , Neoplasia
Lupus like Nephritis	SLE

There are variety of histological entities in HIV immune complex disease which is shown in Table 12 . HIVICK the renal infiltrate is B lymphocytes ,whereas in HIVAN it is T lymphocytes and macrophages**.**

It is more prevalent in Non blacks [58]**.** Clinical spectrum is similar to GN in non- HIV individuals ranging from asymptomatic proteinuria to ESRD [57].The renal lesions may be due to direct result of HIV infection or due to associated coinfection (Hepatitis B or C).

There are common etiological factors for different forms of HIVICK like characteristic cytokine expression, inflammatory infiltrates, renal scarring ,genetic factors and deposition of circulating immune complexes.(CIC 's). CIC 's are formed in all stages of HIV infection due to Immunoglobulins (IgG, IgM, IgA) which binds to circulating HIV antigen (p 24, 8p G1 gp 120)[59] .

The most common ICD in HIV is Membranoproliferative glomerulonephritis. Other lesions has also been described such as membranous nephropathy , IgA nephropathy, Fibrillary GN.

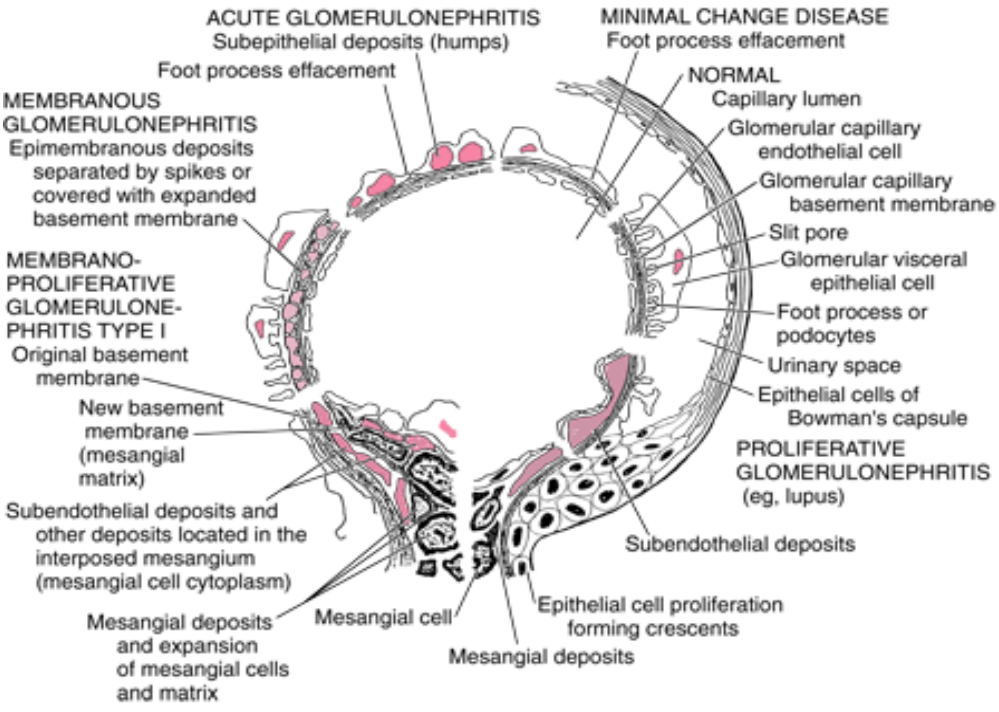
In one postmortem study ,there was report of IgA nephropathy occur in 8 % of the individuals. It can present as hematuria, protenuria

and renal impairment of mild degree and is less in severity than other variants of HIVAN and HIVICK.

Classical features of Lupus like nephropathy is proteinuria ,hematuria, and renal failure which rapidly progress to ESRD. It is more common in African decent males and can usually negative seropositivity for lupus.

Biopsy picture can have focal or diffuse proliferative changes, tubulointerstitial scarring , cresent formation and membranous nephropathy.

Fig 7: ELECTRON MICROSCOPIC FEATURES IN IMMUNOLOGIC GLOMERULAR DISORDERS



There has been reported good response for HIVICK with HAART therapy, glucocorticoids and ACE inhibitors.

HIV ASSOCIATED THROMBOTIC MICROANGIOPATHIES

In 1984, its renal involvement was first described in AIDS patient by Boccia et al. It occurs in two classical forms : TTP (Thrombotic thrombocytopenic purpura) and HUS (Hemolytic Uremia Syndrome). Renal impairment and microangiopathic hemolytic anemia predominates in HUS whereas TTP is a pentad of fever, neurological changes, microangiopathic anemia, thrombocytopenia and renal dysfunction.

HIV associated TTP/HUS is more common in young age group with 80% male predominance.The clinical features are similar to idiopathic form, with worse prognosis and a mortality of 66 to 100%. Proteinurias will be in the nephritic range only and this helps to differentiate it from HIVAN and other immune related nephropathies.

Renal histology similar in both forms which shows platelet and fibrin thrombi are deposited in glomerular capillaries, renal arterioles, and interlobular arteries. Arterial intimal and endothelial cell oedema, mesnagiolysis, microcystic lesions in tubules , fibrinoid necrosis and 'onion skin' lesions are the features as in HIV negative individuals..

Immunofluorescence shows fibrinogen and fibrin in arterioles and fibrinogen, C1Q, C3, C4, IgA, IgM light chains deposits in glomerulus. Electron microscopy shows tubuloreticular inclusions in endothelial cells of blood vessels .

HAART INDUCED NEPHROTOXICITY

HAART Nephrotoxicity is a diagnosis of exclusion , since there is a vast etiological spectrum for HIV induced renal failure. Nephrotoxicity due to ART accounts for 14% of late onset AKI , frequently occurs in first 3 months of starting ART and significant mortality occurs within the first year. HAART can cause various toxic effects to kidney, which can manifest as renal stones, tubular necrosis, ARF or CKD[60].

DART trial was conducted in 3316 symptomatic ART naïve adults with CD4 counts of < 200cells/mm3 . Post initiation with HAART showed an incidence of severe renal dysfunction (GFR <30 mL/mim) occurred in 2.7 % patients who were started with tenofovir –lamivudine plus zidovudine (74%), abacavir (9%) or nevirapine (16%) and the mortality was usually attributed to associated comorbid diseases. Not assessing the function of renal tubules is the important limitation of this study.

Though the overall renal dysfunction have low incidence (0.3 to 2 %)[63], tenofovir is most commonly associated with Fanconi's anemia. Nucleoside analogs have a favorable renal safety profile, with only rare reports of direct toxicity to the renal tubule. Lamivudine and Abacavir have been implicated in Fanconi syndrome and Abacavir have been reported to cause immuno-allergic interstitial nephritis[61].

Table 13 : POTENTIALLY NEPHROTOXIC ANTIRETROVIRALS

Drug	Reported nephrotoxicity	Risk factor(s)
Abacavir	Acute renal failure, interstitial nephritis (rare)	...
Atazanavir	Case reports of nephrolithiasis, interstitial nephritis, reversible renal failure	Not established
Didanosine	Tubular dysfunction (rare)	...
Efavirenz	Single report of hypersensitivity reaction	...
Enfuvirtide	Single report of glomerulonephritis	...
Indinavir	Nephrolithiasis, crystalluria, dysuria, papillary necrosis, acute renal failure	Concomitant treatment with low-dose ritonavir; for nephrolithiasis, urine pH >6, low lean body mass, treatment with trimethoprim-sulfamethoxazole or acyclovir, chronic infection with hepatitis B or hepatitis C virus, warm environmental temperature, high indinavir concentration
Lamivudine	Tubular dysfunction (rare)	...
Ritonavir	Reversible renal failure, but nephrotoxicity not definitely established	Concomitant treatment with nephrotoxic drugs, underlying renal pathology
Stavudine	Tubular dysfunction (rare)	...
Tenofovir	Tubular toxicity, Fanconi syndrome (rare), decreased glomerular filtration rate	Low body weight, impaired baseline renal function, concomitant treatment with potentially nephrotoxic drugs

The major drugs implicated are tenofovir, atazanavir and indinavir [62] which are discussed here.

TENOFOVIR

Tenofovir is the commonly used first line drug along with Lamivudine /Emtricitabine. It is an acyclic phosphonate which is effective against both Hepatitis B and HIV infection ,frequently used in first line HAART regimens. It can cause generalized proximal renal tubular dysfunction (fanconi,s syndrome) which can manifest as : glucosuria ,bicarbonaturia , tubular proteinuria ,uricosuria, aminociduria, uricosuria, and phosphaturia.

It is reported that this tubular toxicity is due to direct tubular cytotoxicity by the drug or due to DNA depletion in mitochondria similar to the use of cidofovir and adefovir . This proximal tubular dysfunction potentially reversible if detected promptly and drug is withdrawn.

Mild toxicity is frequently asymptomatic but severe injury can cause ostemalacia with bone pain and AKI. TDF is reported with a few ,but high risk of AKI, which is nonoliguric and may require dialysis **[63].** However studies shows that there is no significant high risk of proteinuria,CKD and ESRD ,which requires dialysis in HIV patients treated with HAART **[64,65]** .

Table 14 : SCHEME FOR MONITORING PROXIMAL TUBULAR FUNCTION DUTING TENOFOVIR THERAPY : EACS GUIDELINES

SCREENING TESTS	FREQUENCY
1.eGFR	Baseline
2.Urine protein/creatinine ratio	3 monthly for 1 year
3.Urine glucose	Twice monthly thereafter
4.Urine fractional excretion of phosphate	
5.Tubular proteinuria (eg.retinol binding protein)	

Additional survey for proximal renal tubulopathy if any 1-5 present:

- Serum bicarbonate and urinary pH (bicarbonate < 21 and pH >5.5 suggest RTA
- Urinary fractional excretion of uric acid
- Serum potassium and urinary potassium excretion
- Consider DEXA scan if evidence of renal phosphate wasting

Consider stopping if :

- Significant and sustained changes in 1 – 4
- Syndrome of proximal renal tubular acidosis

- Progressive deterioration in tubular proteinuria

Lot of observational studies revealed that TDF induced renal damage is common in patients with multiple comorbid illness and is more frequent in HIV positive patients with associated conditions, shown in table

Table 15 : PREDICTORS OF RENAL FUNCTION DECLINE WITH TENOFOVIR[66]

Preexisting renal impairment
Older age
Advanced HIV disease
Vasculometabolic disease
Concomitant use of nephrotoxic drugs or protease inhibitors
Low body weight
ABCC2 gene (encoding the outward tenofovir transporter MRP-2) polymorphisms

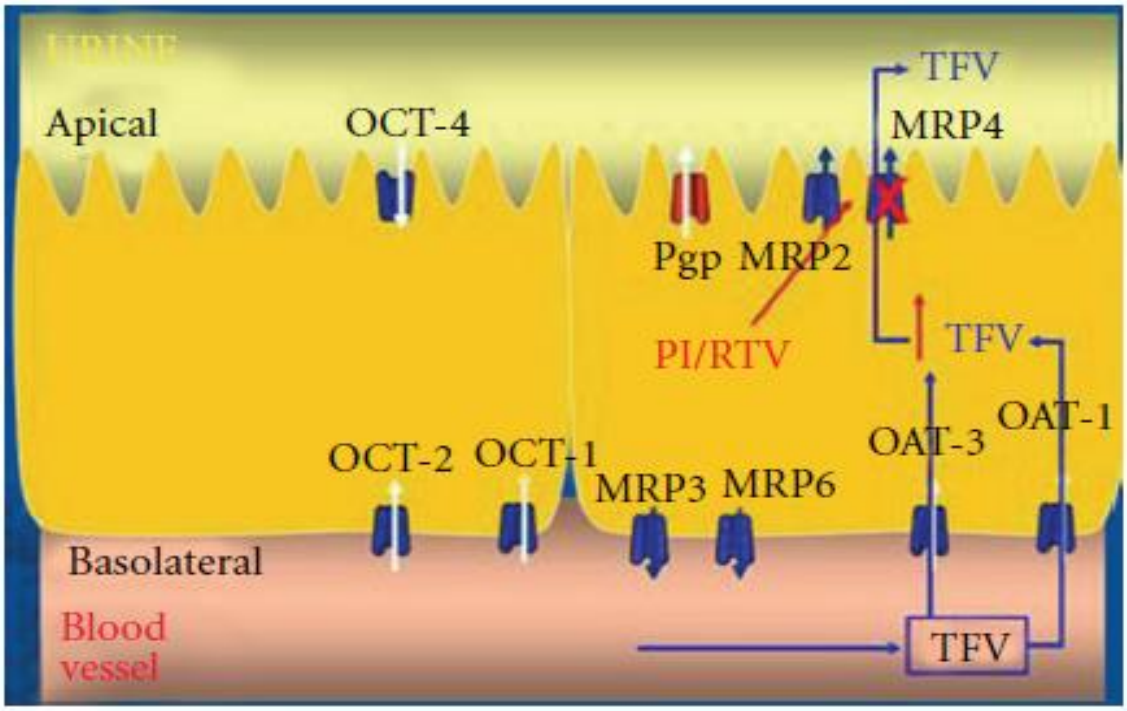
Reduction of eGFR in TDF based regimen have been reported. In the Johns Hopkins study , Tenofovir treated patients have a greater decrease in eGFR than in treated with other regimens (19 vs. 11 mL/min).[67].

Approximately 70% of causes of TDF nephrotoxicity is observed with its concomitant use with Protease inhibitor due to unique mechanism. The MRP4 (multidrug resistance associated protein-4), in the proximal tubules ,which secretes TDF into the urine is inhibited by PI/ritonovir ,which in turn leads to intracellular accumulation of TDF and increased nephrotoxic

effects [68].Concurrent use of NRTI, didanosine is not recommended as it enhance TDF toxicity[57].

In one study consisting of ~140 subjects, there is a greater decrease in GFR of 7-10 mL/ml in tenofovir- boosted PI regimen compared with a tenofovir– nonnucleoside reverse-transcriptase inhibitor or non-Tenofovir -containing regimen over 48 weeks period . [69]

Fig 8 .Mechanism of action of Tenofovir



Tenofovir is predominantly excreted by combination of glomerular filtration and active tubular secretion. It enters into the kidney through organic anion transportess,OAT-1 and OAT-3 from the basolateral side and leaves either via MRP2 and/or MRP4,which are P glycoprotein . MRP4 inhibition by PI/RTV leads to raised intracellular tenofovir levels which may increase its nephrotoxic effects. MRP: multidrug resistant protein; OAT; organic anionic transporter; TFV : tenofovir PI/RTV : ritonavir-boosted protease inhibitor .

TDF is contraindicated in long-term diabetes sufferers, those with uncontrolled hypertension or renal failure and when the estimated glomerular filtration rate is <50 ml/min/1.73 m2.

Other nucleoside analogs like Lamivudine, Abacacir , Stavudine and didanosine have also been reported to cause Fanconi syndrome and nephrogenic Diabetes insipidus in few case reports .

Table 16 : NRTI s dose adjustment for HIV infected patients with renal insufficiency[70]

AGENT	**NORMAL DOSE**	**eGFR (creatinine CL)**
Zidovudine(AZT)	300 mg PO BD	100 mg TDS PO
Lamivudine (3TC)	150 mg PO BD	30-49mL/min=150 mg OD 15-29mL/min=100 mg OD 5-14mL/min=50 mg OD < 5mL/min=25 mg OD
Stavudine (d4T)	30 mg PO BD	26-50mL/min=15 mg BD < 26mL/min=15 mg OD
Emricitabine (FTC)	200 mg PO OD	30-49mL/min=200mg 48hr 15-29mL/min=200mg 72 hr < 15mL/min=200 mg 96 hr
Didanosine (ddl)	<60 kg 250mg OD >60mg 400mg OD	30-59 mL/min=200 mg OD 10-29mL/min=150 mg OD < 10mL/min=100 mg OD

Tenofovir (TDF)	300 mg PO OD	30-49mL/min = 300mg 48 hr 10-29mL/min= 300mg 72 hr <10mL/min= 300 mg once weekly
Tenofovi(TDF)+ Emricitabine (FTC)	1 capsule PO OD	30-49mL/min= 1 tablet every 48hr < 30mL/min not recommended
Abacavir ABC)	300 mg PO BD	No need for dose adjustment

Table 17 : NNRTI's dose adjustment for HIV infected patients with renal insufficiency[70]

AGENT	**NORMAL DOSE**	**eGFR(Creatinine CL)**
Delavirdine (DLV)	400 mg PO TDS	No dose adjustment necessary
Efavirenz (EFV)	600 mg PO OD	No dose adjustment necessary
Efavirenz (EFV)-Tenovofir (TDF)-Emtricitabine(FTC)	600 mg PO OD	Not recommended if CrCl <50 mL/min. Instead use the individual drugs of the fixed-dose combination and adjust TDF and FTC doses .

Nevirapine (NVP)	200 mg PO BD	No dose adjustment necessary

INDINAVIR

In Indinavir therapy , less than 20% of individuals develop indinavir crystalluria. Indinavir renal syndrome (IRS) can manifests silent crytalluria, symptomatic crystalluria with dysuria/ pain in flanks , nephrolithiasis and slow onset scarring tubulointerstitial nephritis associated with pyuria.

In nephrolithiasis, ultrasound KUB shows only mild to moderate obstructive hydrocephalus with no calculi, because of radiolucent stones. Cofactors in IRS are fluid deprivation, acyclovir coadministration, alteration in the dose of indinavir[71]

Tubular crystals, dilatation of tubules and necrosis associated with eosinophillic infiltrates in interstitium and scarring can develop in chronic renal impairment. In 32% of patients on indinavir therapy , persistent leucocyturia is common.

HIVMA- IDSA guidelinesrecommends intake of atleast 1.5 L of water per day iin patients receiving indinavir., and periodic monitoring of urine for pyuria and creatinine should be done in the first 6 months of treatment[71].

Once nephrolithiaisis develops , indinavir therapy can be resumed after treating renal stones ,unless there is associated hypertension, pyuria, a elevated serum creatinine or if rhabdomyolysis present.

Table 18 : Protease,Integrase and Entry inhibitor dose recommendations in renal failure[70] PROTEASE INHIBITOR

AGENT	**NORMAL DOSE**	**eGFR (Creatinine CL)**
Atazanavir (ATV)	400 mg PO OD	No dose adjustment necessary for patients not requiring HD
Fosamprenavir (FPV)	1400 mg PO BD	No dose adjustment necessary
Indinavir (IDV)	800 mg PO TDS	No dose adjustment necessary
Ritonavir (RTV)	600 mg PO BD	No dose adjustment necessary
Lopinavir/ritonavir (LPV/r)	400/100 mg PO BD or 800/200 mg PO OD	Avoid OD dose in patients on HD

Nelfinavir (NFV)	1250 mg BD	No dose adjustment necessary
Saquinavir (SQV)	1200 mg TDS	No dose adjustment necessary
Tiprinavir (TPV)	500 mg PO BD	No dose adjustment necessary

INTEGRASE INHIBITOR

Raltegravir (RAL)	400 mg BD Po	No dose adjustment necessary

ENTRY INHIBITOR

Enfuvirtide (T20)	90 mg s.c BD	No dose adjustment necessary

CCR5 Antagonist

Maraviroc (MVC)	The dose differs based on concomitant drugs and its interactions 150mg, 300mg o r 600mg	CrCl <30mL/min or HD: should reduce Maraviroc and CYP3A inhibitor only if potential benefits overweighs the risk

ATAZANAVIR

Atazanavir is the commonly used once daily protease inhibitor which is well tolerated. Like indinavir it has the potential to crystallize and

form calculi , much less frequently (around 1%). Tubulointerstitial nephritis with atazanavir is correspondingly very rare.

RENAL EFFECTS OF COMMONLY USED DRUGS IN HIV PATIENTS (Non-ARVs) :

Amphotericin B, foscarnet, high dose acyclovir, cidofovir and pentamidine shows nephrotoxic potential an all these should be administered with caution.

- Amphotericin B – Renal tubular acidosis, hypokalemia,bicarbonaturia, decrease serum erythropoietin and increased creatinine value. Liposomal preparation is less nephrotoxic.
- Cidofovir – Dose dependent nephrotoxicity (bicarbonaturia, glycosuria, phosphoturia, nephrogenic diabetes insipidus and polyuria) which is corrected by adequate hydration and probenicid.
- Foscarnet - hypocalcemia, hypophosphatemia, hypomagnesemia, Hyperphosphatemia, hypokalemia and seizures.

Ciprofloxacin, Acyclovir, sulphonamides- intratubular precipitation of crystals leads to ARF .

RENAL DIALYSIS IN HIV POSITIVE PATIENTS

Survival of HIV positive patients with ESRD , who requires either hemodialysis or peritoneal dialysis is comparable to those with HIV negative individuals on dialysis with 1 year survival rates of 74%[72]

Based on CDC recommendations, Renal dialysis can be safely performed in HIV positive patients [73].The choice on the mode of dialysis either peritoneal dialysis or hemodialysis is not predicting the overall survival among HIV patients with ESRD [72]. HIV-1 viral replication is not increased by hemodialysis induced cytokine stimulation.

For hemodialysis , Native arteriovenous fistulae are the preferred access , because of good patency, less complication rates , lower rates of infection than synthetic grafts .In native fistulas, thrombus-free survival for native fistulas is similar to that observed in HIV negative persons.

In HIV-infected patients on peritoneal dialysis, incidence of peritonitis has been reported in case series. In pre –ART era, one large series with 39 HIV patients on peritoneal dialysis observed to have an increased risk of peritonitis due to pseudomonas and fungi.

Peritoneal dialysate fluid also found to have HIV virus, which should be discarded and handled safely . Continuous ambulatory peritoneal dialysis is successfully used in HIV patients, though it is used rarely.

RENAL TRANSPLANTATION

In pre- ART era, there was a varying outcomes in HIV positive renal transplant patients, including long term survival and and rapid progression of HIV because of immunosupression.

In post ART era as there was a dramatic reduction in HIV induced morbidity and mortality, immunosupression is on major concern. In fact, there may be beneficial effect, in immunosupression by reducing the pool of activated T cell targets for new HIV infection, reducing immune activation, inhibiting HIV replication or interacting synergistically with antiretroviral agents.

Few case reports showed that the survival rates are equal in HIV positive and non HIV transplant recipients, however high rates of graft rejects are reported in HIV infected kidney transplant recipients.

PATHOGENESIS OF HIV INFECTION ON KIDNEY

Renal involvement is not well understood in HIV infection . The mechanism for acute renal failure is somewhat similar to in non- HIV infected individuals, so better understood, but for chronic kidney diseases (Immune complex disease, FSGS and microangiopathies) ,the basis remains obscure.

However with recent observations and research , a clearer picture is emerging. It is helpful to highlight several important observations and consolidate various evidences.

Viral activity and replication have been demonstrated in renal tissue. Glomerular epithelium , tubular cell, mesangial and endothelial cells have been shown to demonstrate viral activity and replication.

ROLE OF HIV -1 INFECTION IN AFFECTING RENAL CELLS :

HIV can directly infects the kidneys is evident from the HIV – transgenic mice and its association with advanced HIV disease . Specific gene expression in HIV induces the cellular immune pathways in the host which are responsible for pathogenesis of HIVAN.

The mechanism by which the virus affect the renal cells remains obscure. It may be because of lymphocytes which affect the epithelial cells via transcytosis. Studies showed the genetic variability of gp120, influences the susceptibility of renal epithelial cells for infection in HIV positive individuals.

Another proposed mechanism for renal involvement is due to the lack of microparticles like coreceptors for CCR5 , which is required for virus entry into the cell. An in vitro model , these coreceptors on cell surface helps in allowing virus entry by transferring CCR5 into the cell.

Though in situ hybradiztion and polymerase chain reaction suggested the involvement of both podocytes and epithelial cells ,there is conflicting evidence about the involvement of mesangial cells.

The role of renal dentritic cell in HIV infection was studied. These cells are useful for binding, transfer and dissemination of virus to various

nonlymphoid and lymphoid tissues and also play an important role in infecting renal cells.

An in vitro model suggests the C-type Leptin receptor DEC-205 mediate the internalization of HIV into the renal tubular cells which lack CCR5 ,CXCR4 and CD4.

Thus lot of increasing evidence suggests that the renal cells support viral infection.

ROLE OF VIRAL PROTEINS

The transgenic mice which express particular combinations of viral products as proteins are lacking in pol and gag genes ,so the generation of complete virions are affected.

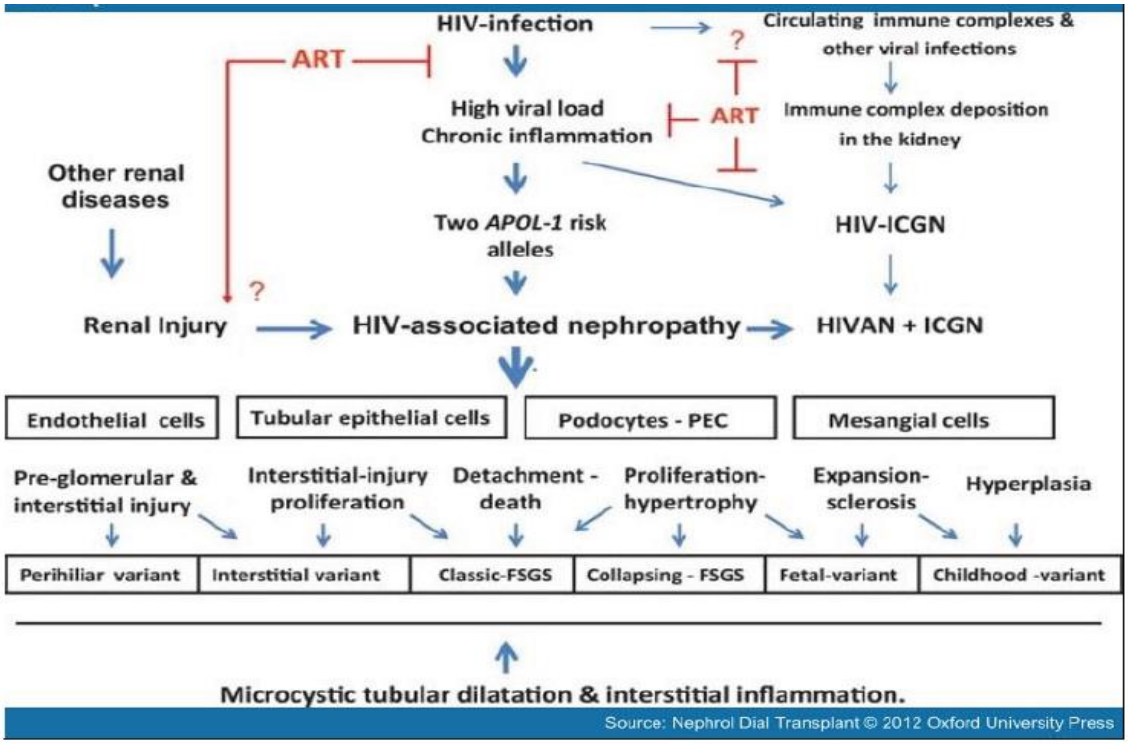
HIV gene products induce direct cell cycle progression, and the apotosis of renal epithelial cells was mediated by caspase activation and Fas up-regulation in both HIVAN specimens and murine models.

In HIVAN , Fas mediated apoptosis is dependent on gp120 and gp160 is responsible for mesangial cell apoptosis and and downregulation of Bcl-2 ,which is a antiapoptotic protein.

HOST FACTORS

HIVAN was first identified in African Americans , the predilection of disease in African Americans is due to increase frequency of ” risk alleles “ which suggest a strong genetic association. The susceptibility focus was identified in Tg26 mouse model , which induce latent perturbations in podocyte gene expression network .Similarly in humans, alleles on MYH9 locus (a functional gene expressed in glomerular podocytes) of chromosome 22 suggests a higher frequency of HIVAN among blacks. However, recent researchers have noted that the MYH9 gene is located next to the APOL-1 gene which is more significantly associated with ESRD than all previously reported variations in MYH9 gene .

Fig 9 : PATHOGENESIS OF HIV INFECTION



Risk factors and pathogenesis of HIV-associated renal diseases. A longstanding high viral load is a major risk factor for the development of HIV-associated renal diseases. Immune activation and chronic inflammation are crucial features driving HIV replication and are additional risk factors for the development of HIV-associated renal diseases. Antiretroviral therapies (ART) block HIV-1 replication, decreasing the viral load and the chronic inflammatory changes (red lines). Untreated individuals of African ancestry carrying two risk variants of the *APOL-1* gene are at very high risk of developing HIVAN. The incidence of HIVAN is reduced in a significant manner with ART. These drugs can also induce renal injury *per se* (red arrow). Other renal diseases may affect the clinical outcome of HIVAN. Some individuals develop HIVAN in combination with immune complex glomerulonephritis (HIVAN + ICGN). The *APOL1* risk variants do not appear to play a direct role in the pathogenesis of HIV-associated immune complex glomerulonephritis (HIV-ICGN). HIV-1 affects several intrinsic renal cell types and induces different histological variants of HIVAN. The tubulointersitial lesions are the most consistent findings seen in patients with HIVAN and can predict an adverse clinical outcome. PEC, parietal epithelial cells; ICGN, immune complex glomerulonephritis.

METHODOLOGY

SOURCE OF STUDY :

Newly diagnosed HIV positive patients who are attending ART clinic and admitting in Medical wards at Coimbatore Medical College Hospital .

DESIGN OF STUDY : Cross sectional study

PERIOD OF STUDY : August 2013 to June 2014

SAMPLE SIZE : 100 patients

STUDY POPULATION :

100 patients who are attending ART clinic and admitting in Medical units at Coimbatore Medical College Hospital were randomly selected as per the inclusion and exclusion criteria. Out of these , 44 were men and 56 were women. The mean age of subjects was 40.8 years with a range of 20-81 years. Written informed consent was obtained from each HIV positive patients enrolled in the study .

INCLUSION CRITERIA :

All newly diagnosed adult HIV positive patients as per the NACO guidelines , who was started on HAART and who are attending ART clinic and also patients who were admitted in Medical units at Coimbatore Medical College Hospital.

EXCLUSION CRITERIA :

- Patients with Chronic renal failure
- Patients with diagnosed systemic causes of renal diseases

(eg., SLE ,Systemic Sclerosis, Rhematoid arthritis, and other rheumatological & connective tissue disorders)

- Patients who are known Diabetic or Hypertensive or any other comorbid illness .
- Patients with associated Hepatitis B/ C virus infection
- Pregnant women and children age less than 15 years
- Patients with poor adherence (> 80 %)
- Patients receiving other nephrotoxic drugs / NSAIDS.
- Pregnancy

DATA COLLECTION

The 100 newly diagnosed HIV positive patients were included in the study. Detailed history – including duration of disease, any past history of antiretroviral drug and other medications , treatment regimen started , WHO staging of the HIV disease were obtained . Patients were examined in detailed for assessing any symptoms and signs of renal failure . Blood samples were taken for screening baseline renal function for urea, creatinine and also for CD4 count . Baseline eGFR was calculated using Cockgroft – Gault equation . Patients were followed up over a period of 10 months and any opportunistic infections developed among patients during study period was noted. At the end of 10 months, patients were assessed for Urea , Creatinine , CD4 counts by drawing blood samples and eGFR was calculated using CG formula. Urine routine and USG KUB was done .

STATISTICAL ANALYSIS :

All the dates were entered in a data collection sheet in an Excel format and analysed using SPSS Software. Numerical values were reported using mean and standard deviation or median. Categorical values are reported using number and percentages. Probability value (p) value less than 0.05 was considered a statistically significant.

RESULTS

The present study is a prospective study . Cross- sectional data for 100 patients diagnosed to have HIV infection who was attending ART clinic and Medical units at CMCH during the period of August 2013 to June 2014 , were recruited for the purpose of this study.

TABLE 19 : CHARACTERISTIC OF STUDY POPULATION

CHARACTERISTICS
TOTAL NO OF SUBJECTS - 100
AGE - 20 - 81
MALE - 44
FEMALE - 56
STAGING of KIDNEY DAMAGE BASED ON eGFR (END of Study)
GFR Normal >90 ml/min/1.73m^2 - 21
GFR Mild 60 – 90 ml/min /1.73m^2 - 37
GFR Mod – Sev < 60 ml/min/1.73m^2 - 42
WHO CLINICAL STAGING AFTER ART
T1 - 67
T2 - 7

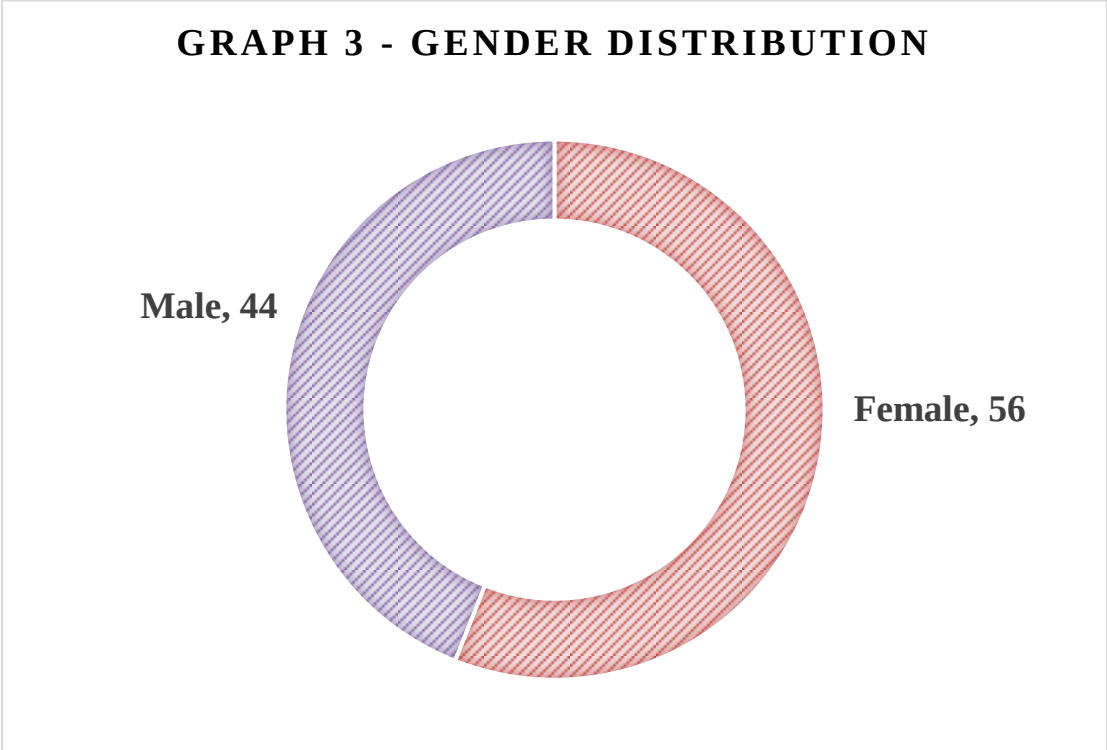
T3	**- 12**
T4	**- 14**
HAART REGIMEN	
TLN	**- 28**
TLE	**- 42**
ZLN	**- 22**
ZLE	**- 8**

A total of 100 patients were selected for the study .Of the 100 HIV infected patients , starting ART at CMCH ,44 males and 56 females. Among them patients were distributed across the age spectrum of 20 to 81 years. Females accounts for 56% of study population and the mean age was 40.08. The patients were distributed in all the clinical stages of HIV disease from T1 to T4.

And four types of regimen was taken by the patients TLN (28), TLE(42), ZLN (22) ,ZLE (8). Out of 100 patients , at the end of study 21 % patients with Normal GFR (>90), 37% with mild reduction (60-90) and 42% with mod- severe reduction in eGFR (<60), ten months after initiating ART, with majority of GFR decline in Tenofovir based regimens .

TABLE 20 : GENDER DISTRIBUTION

Gender	Frequency	%
Female	56	56
Male	44	44
Total	100	100



In this present study , majority are females with 56% of study population and males constitutes 44% of study population.

TABLE 21 : RELATIONSHIP BETWEEN GENDER AND eGFR_E

Relationship between Gender and eGFR_E				
	eGFR_E			
SEX	**Mean**	**Minimum**	**Maximum**	**No of Cases**
Female	64.91	24	129	56
Male	74.83	32.4	143	44
Total	69.28	24	143	100

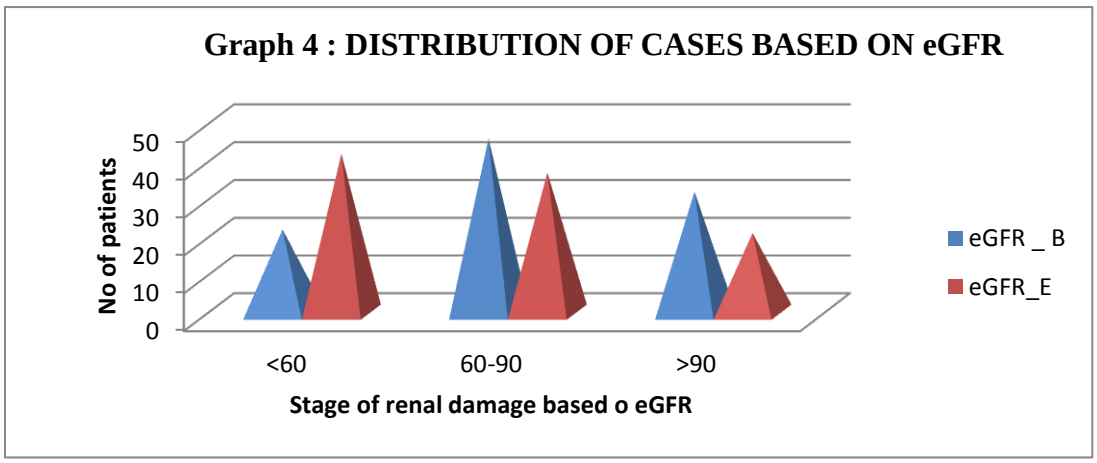
ANOVA					
eGFR_E					
	Sum of Squares	df	Mean Square	F	P Value
Between Groups	2426.471991	1	2426.471991	3.6773460	**0.06**
Within Groups	64664.63995	98	659.8432648		
Total	67091.11194	99			

The average eGFR for female is 64.91 and for male is 74.83

The ANOVA test indicates that the difference of average in eGFR between male and female is not statistically significant

TABLE 22 : DISTRIBUTION OF CASES ACCORDING TO ESTIMATED GLOMERULAR FILTRATION RATE BEFORE AND AFTER ART

Category (eGFR ml/min)	eGFR_ B (Baseline)	eGFR_E (End of 10th mon)	Difference eGFR (B-E)
< 60(Mod-sev)	22	42	20
60-90 (Mild)	46	37	9
>90 (Normal)	32	21	11
Total	100	100	40

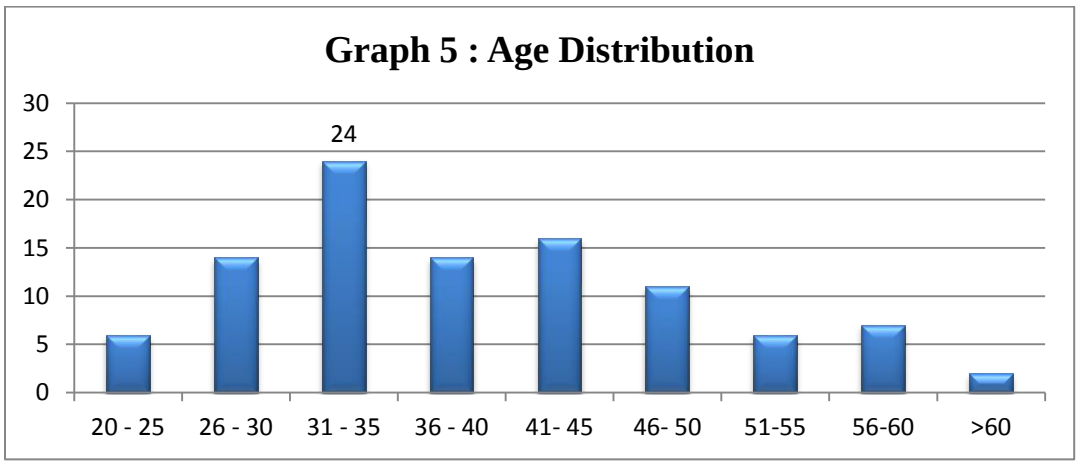


The overall average mean eGFR at the end of study in this sample is 69.28

In this study , before starting ART most patients , 46 % were in 60-90 category and 32% were in >90 category and at the end of study after HAART initiation , 79% of patients were in eGFR < 90 ml/min . Of which , 42 % in <60 (mod – severe) and 37% in 60-90 eGFR(mild reduction) . Approximately 20 % of patients with normal baseline eGFR falls into severe decline in eGFR after ART introduction .

TABLE 23 : AGE DISTRIBUTION

Age in years	Total
20 – 25	6
26 -30	14
31 -35	24
36 – 40	14
41 – 45	16
46 – 50	11
51- 55	6
56 – 60	7
>60	2



Most of the patients in the study are in the age group of 31 to 45 (3rd and 4th decade) with majority in 31 – 35 (24 %). The mean age in the study was 40.02.

TABLE 24 : RELATIONSHIP BETWEEN AGE AND eGFR

Relationship between AGE and eGFR_E (No of Cases)					
	eGFR_E	**< 60**	**60 -90**	**> 90**	**Total**
AGE	20 - 25	3	1	2	6
	26 -30	4	4	6	14
	31 -35	11	7	6	24
	36 - 40	6	5	3	14
	41 - 45	7	6	3	16
	46 - 50	4	7	0	11
	51 - 55	1	5	0	6
	56 - 60	4	2	1	7
	> 60	2	0	0	2
	Total	42	37	21	100

Symmetric Measures					
		Correlation Value	Asymp. Std. Errora	Approx. Tb	**(P Value)**
Interval by Interval	Pearson's R	-0.20	0.09	-2.025	0.046
Ordinal by Ordinal	Spearman Correlation	-0.16	0.099	-1.57	0.12
N of Valid Cases		100			

The correlation between eGFR_E and AGE is negative .It appears almost significant with a P value of 0.046. . Majority decline in eGFR occur in the age group of 31- 35 with category < 60 in 11 patients (26%).

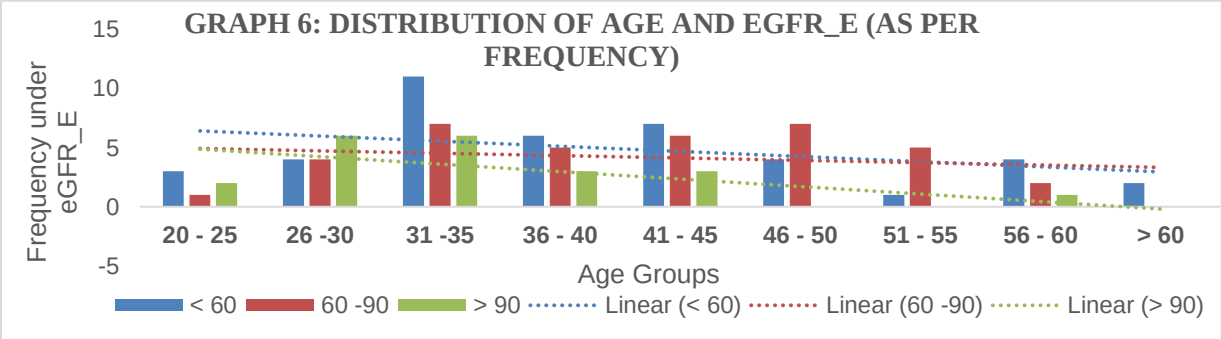


TABLE 25 : COMPARISON BETWEEN eGFR ACROSS AGE

Dependent Variable	Mean Age	(I) eGFR E	(J) eGFR_E	Mean Difference (I-J)	Std. Error	**P Value**
AGE	41.12	< 60	60-90	-0.935	2.405	0.92
	42		> 90	6.881*	2.85	**0.046**
	42.05	60-90	< 60	0.935	2.405	0.92
	37		> 90	7.816*	2.914	**0.023**
	34.24	> 90	< 60	6.881*	2.85	**0.046**
	21		60-90	-7.816*	2.914	**0.023**

This table indicates that at eGFR (at the end of study) greater than 90 which is normal kidney function , has significantly lower average age when compared to other two categories, where there has mild to moderate kidney damage occurs . However between the categories of less than 60 and 60-90, the average age levels do not seems to be significant.

So , this study shows that significant renal damage can occur in the higher age group of when compared to lower average age groups.

TABLE 26 : COMPARISON OF eGFR_E ACROSS WEIGHT

Dependent Variable	Mean WEIGHT (kg)	(I) eGFR_E	(J) eGFR_E	Mean Difference (I-J)	Std. Error	**P Value**
WEIGHT (KG)	46.69	< 60	60-90	-3.174	1.355	0.055
	42		> 90	-2.786	1.606	0.198
	49.86	60-90	< 60	3.174	1.355	0.055
	37		> 90	0.389	1.642	0.97
	49.48	> 90	< 60	2.786	1.606	0.198
	21		60-90	-0.389	1.642	0.97

This table indicates that between either of this three categories ,the weight does not appear to be significantly different and P value is > 0.05

In this present study, the mean weight of the patients were 48.45 Kg , with a minimum of 27 Kg and a maximum of 58 Kg.

TABLE 27 : COMPARISON OF eGFR_E ACROSS UREA.

Dependent Variable	Mean UREA_E	(I) eGFR_E	(J) eGFR_E	Mean Difference (I-J)	Std. Error	P Value
UREA_E (End of study)	29.9	< 60	60-90	2.418	1.174	0.104
	42		> 90	3.381*	1.391	**0.044**
	27.49	60-90	< 60	2.418	1.174	0.104
	37		> 90	0.963	1.422	0.777
	26.52	> 90	< 60	-3.381*	1.391	**0.044**
	21		60-90	-0.963	1.422	0.777

This table indicates that between less than 60 and greater than 90 eGFR_E, the average levels of Urea_E is different. Average levels of UREA_E is higher for < 60 eGFR_E as compared to >90 eGFR_E with P value of 0.044 .

No significant difference of levels of Urea is indicated ,between 60-90 category and < 60 category of eGFR and also between 60-90 and > 90 category.

Mean urea was 28.3 mg/dl with minimum of 16 and maximum of 44.

TABLE 28 : COMPARISON OF eGFR ACROSS CREATININE

Dependent Variable	Mean CREATINE	(I) eGFR_E	(J) eGFR_E	Mean Difference (I-J)	Std. Error	**P Value**
CREATININE (End of study)	1.26	< 60	60-90	.3349*	0.0566	**0**
	42		> 90	.5476*	0.0671	**0**
	0.93	60-90	< 60	-.3349*	0.0566	**0**
	37		> 90	.2127*	0.0686	**0.007**
	0.71	> 90	< 60	-.5476*	0.0671	**0**
	21		60-90	-.2127*	0.0686	**0.007**

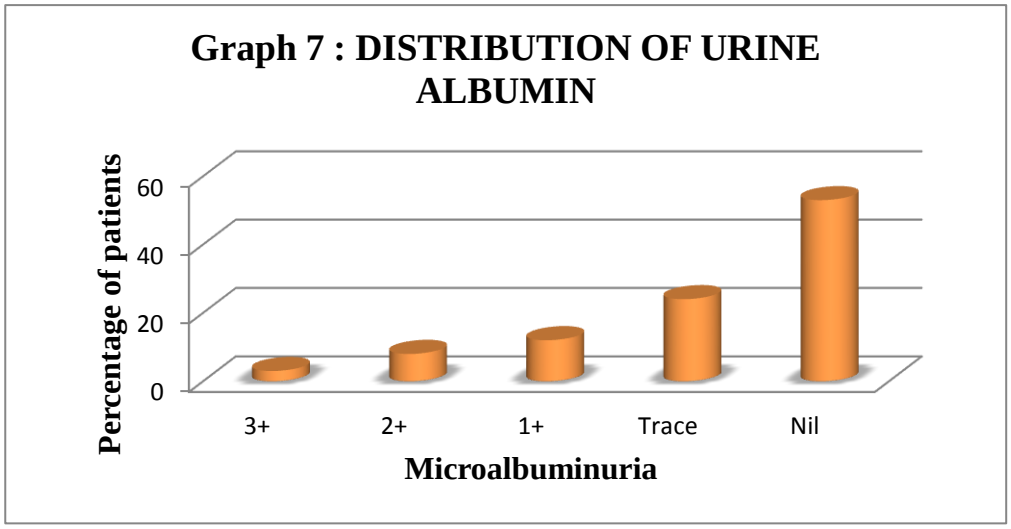
This table indicates that between all three categories of eGFR at the end of study , the average levels of Creatinine are different

In other words , average levels of creatinine is significantly higher for <60 eGFR as compared to 60-90 and >90 eGFR levels. Also creatinine average is higher for 60-90 eGFR_E as compared >90 eGFR_E levels. In the present study , it shows that increase in creatinine value from baseline is directly proportional to decline in eGFR from 90 – 60 and < 60.

Mean creatinine value is 1.028 with minimum of 0.5 and maximum of 1.8.

Table 29 : DISTRIBUTION OF CASES ACCORDING TO URINE ALBUMIN

Microalbuminuria	No of patients	Percent
Nil	53	53%
Trace	24	24%
1+	12	12%
2+	8	8%
3+	3	3%
Total	100	100.0

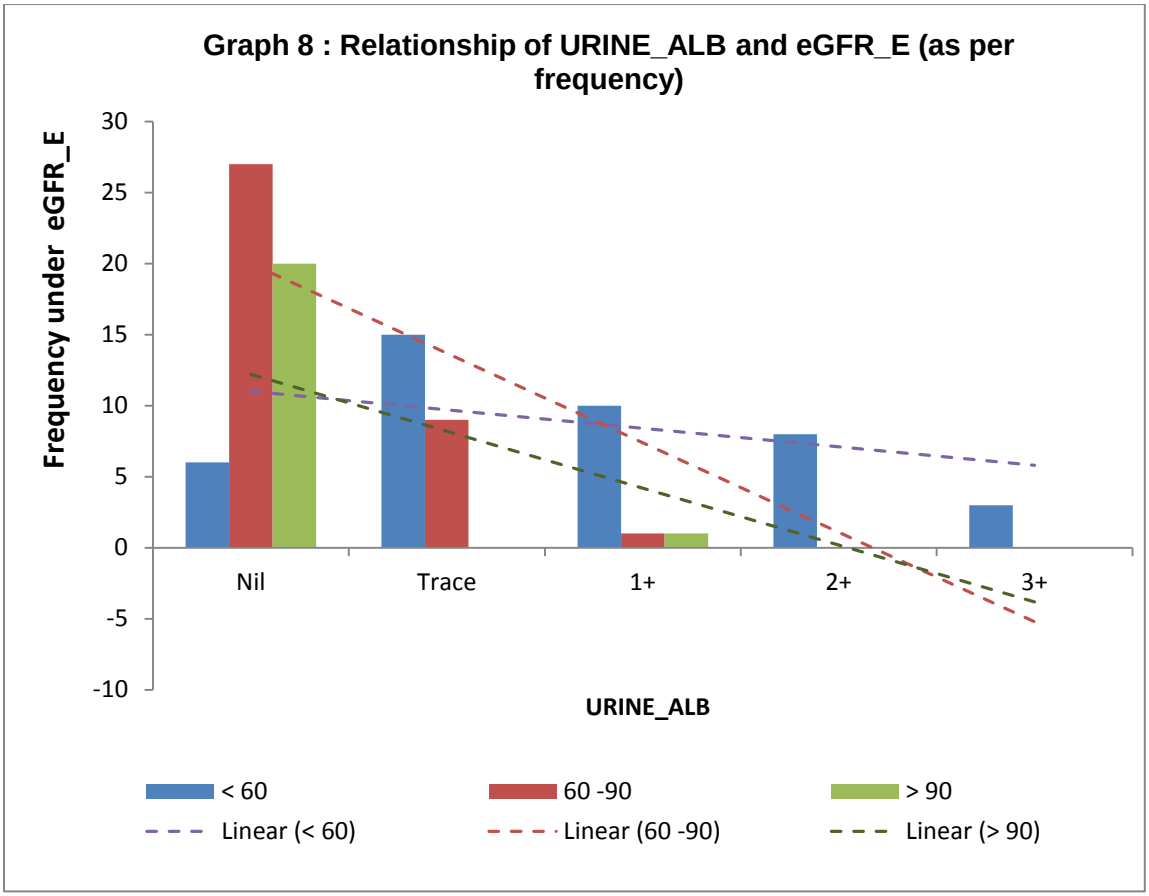


In the present study , albuminuria was noted in 47 patients(47%).Of the 47 ,who had albuminuria ,24 had Trace, 12 had 1+,8 had 2+ and 3 had 3+ albuminuria.

TABLE 30 : CORRELATION BETWEEN URINE ALBUMIN AND eGFR_E

Relationship between URINE_ALB and eGFR_E (No of Cases)					
	eGFR_E	**< 60**	**60 -90**	**> 90**	**Total**
Urine ALB	Nil	6	27	20	53
	Trace	15	9	0	24
	1+	10	1	1	12
	2+	8	0	0	8
	3+	3	0	0	3
Total		42	37	21	100

Symmetric Measures					
		Value	Asymp. Std. Errora	Approx. Tb	Approx. Sig.
Interval by Interval	Pearson's R	-0.609	0.049	-7.599	0.000
Ordinal by Ordinal	Spearman Correlation	-0.682	0.058	-9.243	0.000
N of Valid Cases		100			



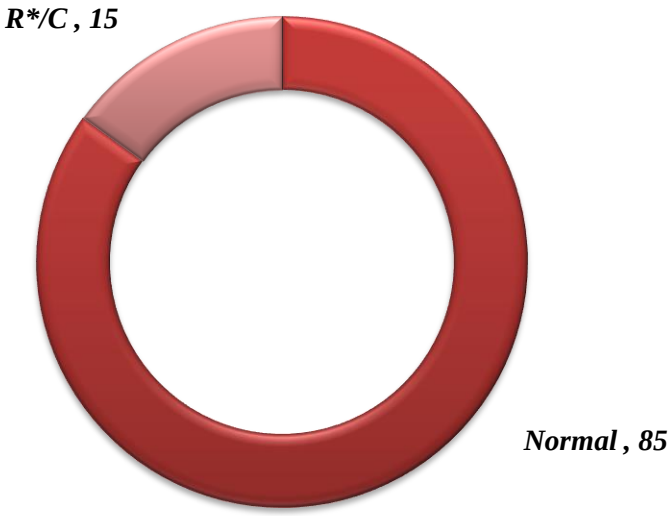
In the present study , there was a negative correlation between Urine albumin and eGFR at the end of study and the P value is significant 0.00 .

This study shows that, as the grades of urine albumin increases, eGFR declines . Category with eGFR < 60 ml/min shows high albuminuria with 23% in 1+ ,19% in 2+ and 7% in 3+ range.

TABLE 31 : DISTRIBUTION OF USG –KUB

Distribution of USG_KUB		
USG_KUB	**Frequency**	**Percent**
Normal	85	85%
R*/C	15	15%
Total	100	100%

Graph 9 : USG_KUB DISTRIBUTION

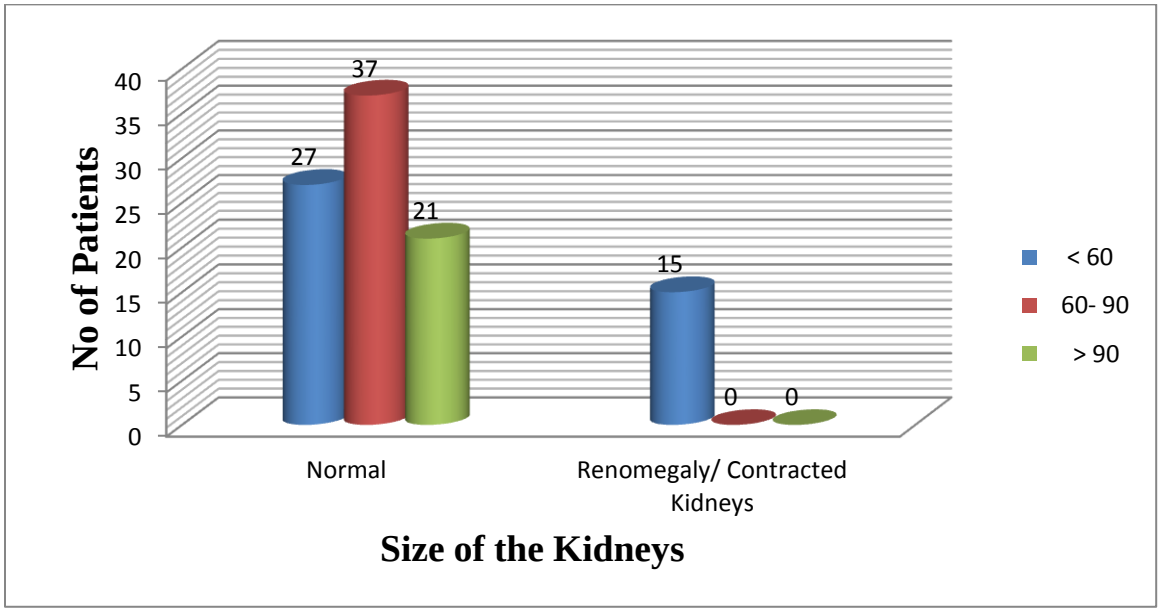


In the present study , renomegaly / contraceted kidney was found in 15 patients (15%) and 85 patients (85%) had normal sized kidneys .

TABLE 32 : DISTRIBUTION OF USG- KUB ACROSS eGFR_E.

eGFR_E				
USG_KUB	**< 60**	**60 -90**	**> 90**	**Total %**
Normal	27	37	21	85
Renomegaly/ Contracted	15	0	0	15
Total	42	37	21	100

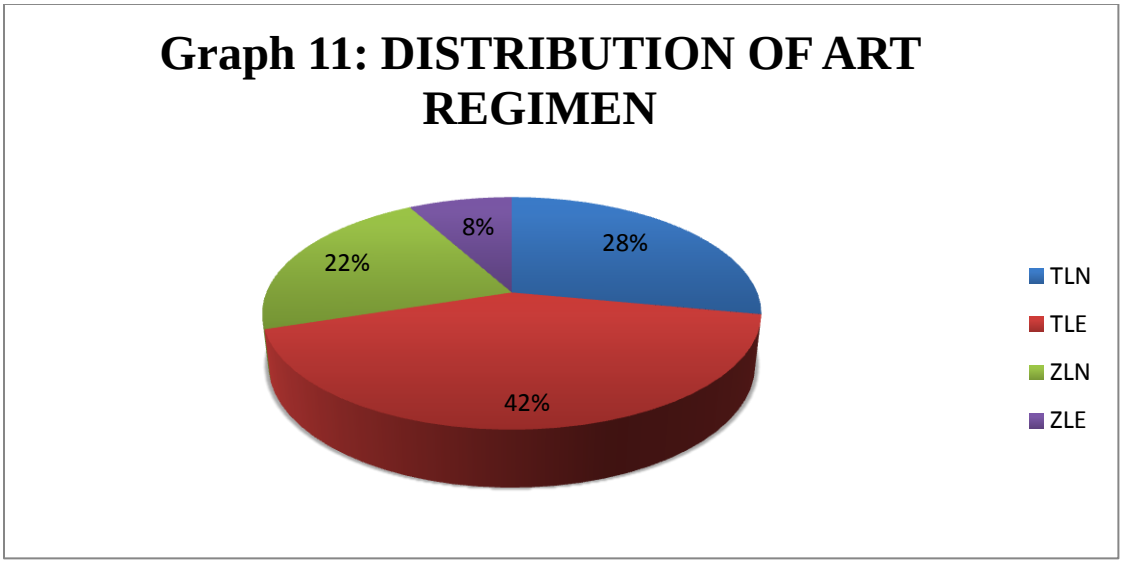
Graph 10:



Among 15 % of patients with abnormal kidney size , almost all patients were come under the category of e GFR < 60 ml/min.

Table 33 : DIFFERENT TYPES OF ART REGIMEN TAKEN BY THE PATIENT DURING STUDY

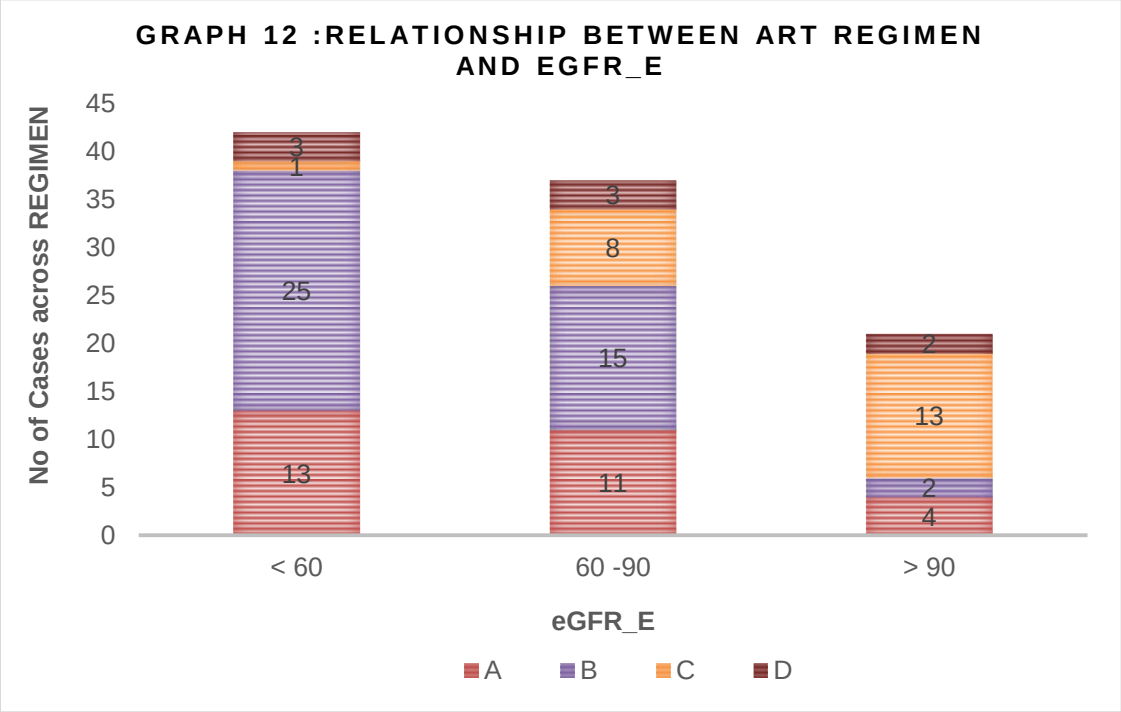
REGIMEN	NO OF PATIENTS	PERCENTAGE
TLN (A)	28	28%
TLE (B)	42	42%
ZLN (C)	22	22%
ZLE (D)	8	8%
TOTAL	100	100%



In present study , 4 types of ART regimen was taken up by the patients with TLN (28%) , TLE (42%), ZLN (22%) and ZLE (8%) . Majority of patients are in Tenofovir based regimen .

TABLE 34 ; RELATIONSHIP BETWEEN THE ART REGIMEN AND eGFR_E DURING STUDY

Relationship between REGIMEN and eGFR_E (No of Cases)							
	eGFR_E	**< 60**	**60 -90**	**> 90**	**Total**	**%**	
REGIMEN	TLN (A)	13	11	4	28	28%	
	TLE (B)	25	15	2	42	42 %	**70%**
	ZLN (C)	1	8	13	22	22%	
	ZLE (D)	3	3	2	8	8%	**30%**
Total		42	37	21	100	100%	



Among the ART regimen used in this study , Tenofovir based regimen (AB) accounts for 70 cases (70%) and Zidovudine based regimen (CD) accounts for 30% of cases.

Relationship between REGIMEN and eGFR_E						
	eGFR_E					
REGIMEN	**eGFR_E**	**Mean**	**Mini**	**Max**	**No of Cases**	**% of Cases on Total Sample**
AB Tenofovir based	<= 90	56.7	24.0	88.4	64	64%
	> 90	103.5	90.6	124.6	6	6%
	Total	60.7	24.0	124.6	0	70%
CD Zidovudine based	<= 90	67.8	37.8	87.6	15	15%
	> 90	110.6	94.6	143.0	15	15%
	Total	89.2	37.8	143.0	30	30%
Total	<= 90	58.8	24.0	88.4	79	79%
	> 90	108.6	90.6	143.0	21	21%
	Total	69.3	24.0	143.0	100	100%

eGFR_E Tukey HSD	**Multiple comparisons Regimens**			
(I) REGIMEN_2_eGFRE_2	(J) REGIMEN_2_eGFRE_2	Mean Difference (I-J)	Std. Error	**P Value**
AB <= 90	AB > 90	-46.76	6.79	0.00
	CD <= 90	-11.12	4.56	0.08
	CD > 90	-53.92	4.56	0.00
AB > 90	AB <= 90	46.76	6.79	0.00
	CD <= 90	35.64	7.68	0.00
	CD > 90	-7.16	7.68	0.79
CD <= 90	AB <= 90	11.12	4.56	0.08
	AB > 90	-35.64	7.68	0.00
	CD > 90	-42.80	5.81	0.00
CD > 90	AB <= 90	53.92	4.56	0.00
	AB > 90	7.16	7.68	0.79
	CD <= 90	42.80	5.81	0.00

This multiple comparisons table indicates

Regimen AB with eGFR <90 is having significantly lower eGFR as compared to AB with eGFR > 90

Regimen AB with eGFR < 90 is having significantly lower eGFR as compared to CD with e GFR .90

Regimen AB with eGFR > 90 is having significantly lower eGFR as compared to CD with e GFR < 90

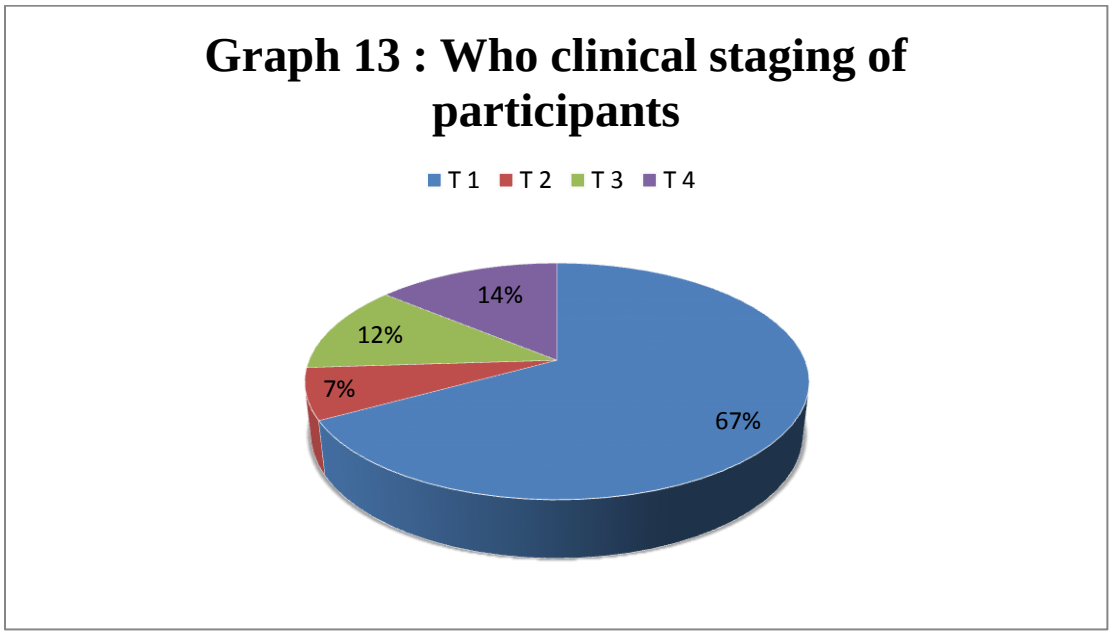
Regimen CD with e GFR < 90 is having significantly lower GFR as compared to CD with eGFR > 90

TENOFOVIR BASED REGIMEN TREATED PATIENTS HAS SIGNIFICANTLY LOWER EGFR COMPARED TO ZIDOVUDINE BASED REGIMEN .

TABLE 35 : WHO CLINICAL STAGING OF PARTICIPANTS IN STUDY

STAGE	No of patients	%
T1	67	67%
T2	7	7%
T3	12	12%
T4	14	14%
Total	**100**	**100%**

Graph 13 : Who clinical staging of participants

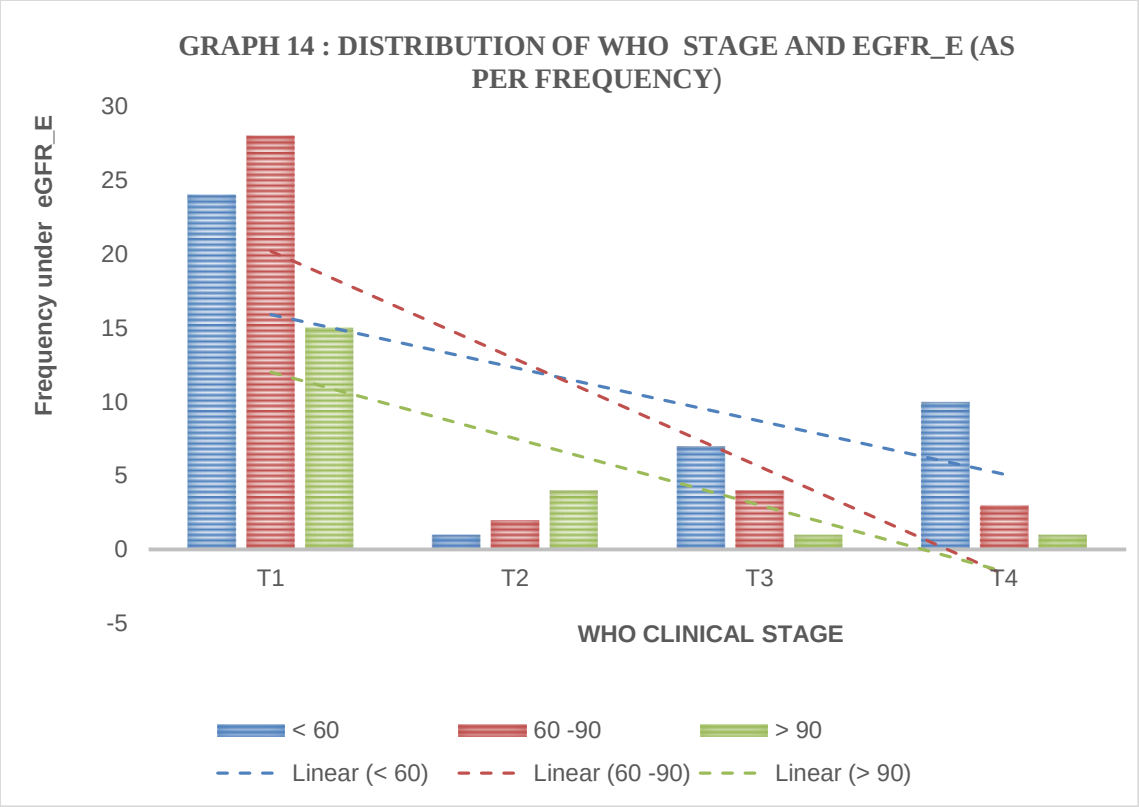


In this present study , majority of HIV patients were in WHO clinical stage T1 (67%) , and 7 % in T2 , 12% in T3 and and 14 % in T4.

TABLE 36 : CORRELATION BETWEEN WHO CLINICAL STAGING AND eGFR_E

Relationship between WHO CLINICAL STAGE and eGFR (No of Cases)					
	eGFR_E	**< 60**	**60 -90**	**> 90**	**Total**
STAGE	T1	24	28	15	67
	T2	1	2	4	7
	T3	7	4	1	12
	T4	10	3	1	14
Total		42	37	21	100

Symmetric Measures					
		Correlation Value	Asymp. Std. Error	Approx. Tb	**P Value**
Interval by Interval	Pearson's R	-0.239	0.088	-2.436	0.017
Ordinal by Ordinal	Spearman Correlation	-0.203	0.096	-2.054	0.043
No of Valid Cases		100			

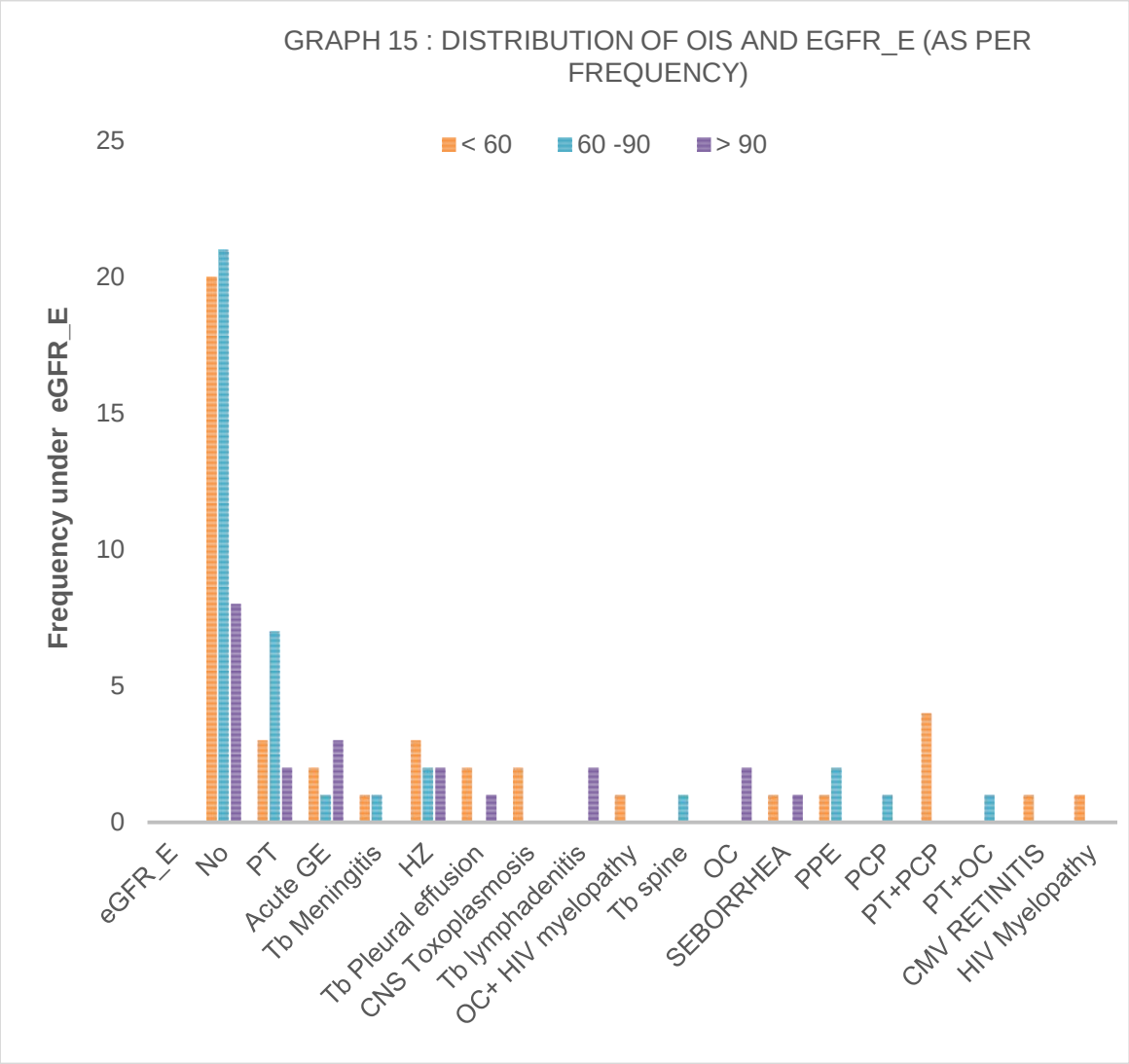


In the present study , there was a negative correlation between WHO clinical stage and eGFR and the P value is 0.017 which is significant . As the stage of the disease increases decline in eGFR also increases . In T4 stage out of 14 cases ,10 cases (71%) are in < 60 category . but in T1 out of 67 ,only 24 cases (36%) are in < 60 category.

TABLE 37 : CORRELATION BETWEEN OI' S AND e GFR_E

Relationship between OIS and eGFR_E (No of Cases)					
	eGFR_E	**< 60**	**60 -90**	**> 90**	**Total**
OIS	No	20	21	8	**49**
	PT	3	7	2	**12**
	Acute GE	2	1	3	**6**
	Tb Meningitis	1	1	0	**2**
	HZ	3	2	2	**7**
	Tb Pleural effusion	2	0	1	**3**
	CNS Toxoplasmosis	2	0	0	**2**
	Tb lymphadenitis	0	0	2	**2**
	OC+ HIV myelopathy	1	0	0	**1**
	Tb spine	0	1	0	**1**
	OC	0	0	2	**2**
	SEBORRHOEA	1	0	1	**2**
	PPE	1	2	0	**3**
	PCP	0	1	0	**1**
	PT+PCP	4	0	0	**4**
	PT+OC	0	1	0	**1**
	CMV RETINITIS	1	0	0	**1**
	HIV Myelopathy	1	0	0	**1**
Total		**42**	**37**	**21**	**100**

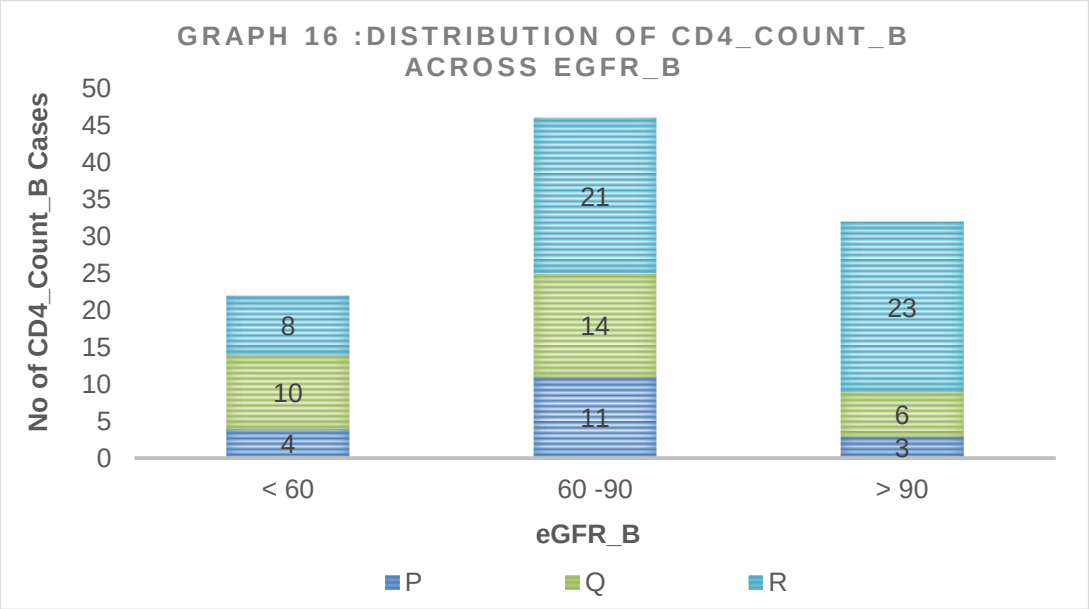
Symmetric Measures					
		Correlation Value	Asymp. Std. Error	Approx. Tb	**P Value**
Interval by Interval	Pearson's R	-0.091	0.094	-0.908	**0.366**
Ordinal by Ordinal	Spearman Correlation	-0.029	0.102	-0.291	**0.772**
No of Valid Cases		100			



In the present study ,there was no correlation between opportunistic infections and eGFR at the end of study is visible from the table .Also P value is not significant.

TABLE 38 : CORRELATION BETWEEN BASELINE CD4 COUNT AND eGFR

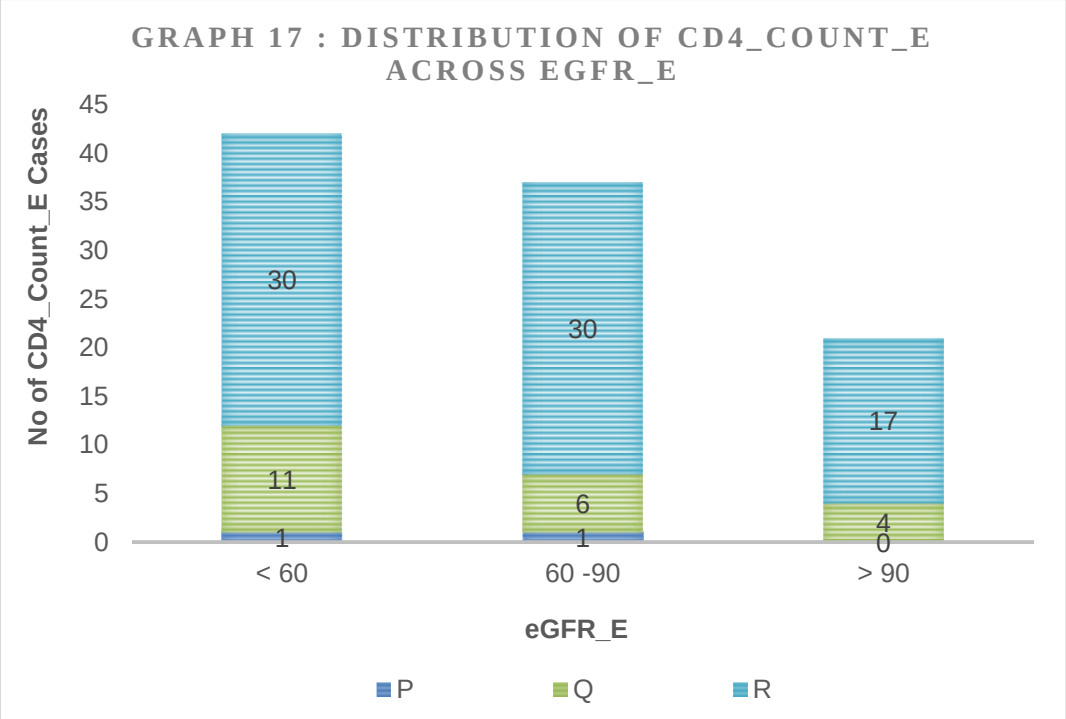
Relationship between CD4_COUNT_B and eGFR_B (No of Cases)						
		eGFR_B			Total	%
		< 60	**60 -90**	**> 90**		
CD4_COUNT_B	P (<100)	4	11	3	18	18%
	Q(100-200)	10	14	6	30	30%
	R(>200)	8	21	23	52	52%
Total		22	46	32	100	



In this study, baseline CD4 count less than 200 was noted in 48% , Of these 18 patients had < 100 count and 30 patients had 100 to 200 count .Majority of patients with decline in CD4 count <200 are in eGFR 60-90 category.

TABLE 39 : CORRELATION BETWEEN CD4 COUNT AND eGFR AT THE END OF STUDY

Relationship between CD4_COUNT_E and eGFR_E (No of Cases)						
		eGFR_B			Total	
		< 60	**60 -90**	**> 90**		
CD4_COUNT_E	P(<100)	1	1	0	2	2%
	Q(100-200)	11	6	4	21	21%
	R (>200)	30	30	17	77	77%
Total		42	37	21	100	



In this study , CD4 count at the end of study which is less than 200 were noted in 24 % of patients .Of which 2 patients had < 100 and 21 patients had 100 to 200 CD4 counts. Majority of patients with decline in CD4 count <200 are in less than 60 eGFR category.

DISCUSSION

A total of 100 patients diagnosed to have HIV infection were recruited for this study . They were recruited from ART clinic (90% data) and Medical Units at Coimbatore Medical College Hospital during the period of August 2013 to June 2014 over 10 months after fulfilling inclusion and exclusion criteria.

In 100 patients , about 79% of HIV infected patients starting ART in our setting at CMCH had evidence of renal dysfunction , with reduced eGFR of grade 2 (60-90ml/min) in 37 % and eGFR grade 3 or less (<60ml/min) in 42 % of study population. These patients had no known preexisting renal disease or risk factors for renal dysfunction aside from HIV infection. These high rates of renal dysfunction were confirmed by the finding that over 47 % of patients had detectable microalbuminuria.

The finding that majority of renal dysfunction may be present in HIV –1 infected outpatients initiating ART has important ramnifications given the increasingly widespread use of Tenofovir , a first line regimen recommended by WHO with known renal toxicity. In our study 70% of patients were in Tenofovir based regimen.

Our data suggest that low eGFRs which we observed reflect the true renal disease because patients with low eGFRs were also more likely to have high grade albuminuria .

Age and Gender distribution of cases :

Most of the patients in the present study were females in the age group of 31-40 (56%) and the mean age of the patients in the present study was 40.08

STUDY	**MEAN AGE**	**GENDER PREDOMINANCE**
Oche O.Agbaj.et.al	38.8	Female
Rawlings Mb et.al	37.9	Male
Longo Ab et.al	43	Female
Lene Ryam et.al	39	Male
DART trial [74]	37	Female

The mean age was more or less similar in all these studies .

Distribution of cases according to eGFR

In the present study , the baseline eGFR in majority of patients comes under category 60-90 and ten months after intiation of HAART , majority of patients falls under the category < 60ml/min . 20 % has fall down from >90 and 60 to 90 eGFR to < 60 ml/min eGFR following ART therapy . So, Overall prevalence of renal dysfunction is 20% after ART. This indicates that ART use has impact on renal function which can be predicted by decline in eGFR. Percentage and mean decline in eGFR is compared to other trials .

STUDY	**PREVALENCE OF RENAL DYSDUNCTION**
Msango et.al , Tanzania	25%
Chukwuonye et.al[75]	50%
Kenya and Uganga Trial[76]	23%
DART trial	7%

Distribution of cases according to urine albumin :

In the present study albuminuria was noted in 47% . Among these 36 % had insignificant albuminuria , 2+ in 8% and 3+ in 3 % albuminuria .

The incidence of albuminuria in the present study was comparable to that reported with various other studies

Distribution of cases according to USG – KUB:

In the present study 15 % of patients have abnormal sized kidney ,and 85% have normal size kidneys .

According to the study by De Fiori et al., Renomegaly was present in 20% of patients . The present study , in contrary to the above mentioned study has not proven the cases of HIVAN (though signs and symtoms were present) , because renal biopsy was not done .

Distribution of cases according to type of ART regimen :

In the present study , majority of patients 70% were in Tenofovir based Regimen which included 28% in TLN and 42% in TLE .

Rest of the 30% were in Zidovudine based regimen which includes 22% in ZLN and 8% in ZLE. Msango et al . , Tanzania study also shows the use of Tenofovir as the first line regimen in HIV outpatients group as recommended by WHO ,though it has nephrotoxic potential .

Relationship between ART regimen and eGFR at the end of study :

In the present study ,Tenofovir based regimen (Total no.70) contributed to most of the moderate to severe decline in eGFR with 64 % of patients are under < 90 ml/min , with 38% in < 60 ml/min category . These results are comparable to other studies.

In the DART trial the incidence of grade 3 or 4 decreased eGFR was 1.7% for participants on TDF . These changes occurred in a median of 14 weeks after starting ART

In Western studies, incidence ranged from 1.3% changes in creatinine clearance and serum creatinine elevations in ART-experienced patients after starting TDF [55], to a cumulative incidence rate of a confirmed GFR <70 ml/min of 1.18 per year of TDF use (95% CI: 1.12; 1.25) in patients with normal baseline renal function (eGFR _90 ml/min)

In a study in Senegal more patients on TDF moved from mild (60-90 ml/min/1.73 m2) to moderate renal impairment (30 - 60 ml/min/1.73 m2) after a year, compared to patients not on TDF with a rate ratio of transition from mild to moderate renal impairment of 2.74 in patients receiving TDF.

In a Copenhagem study by Lene Ryom et al. with total 22,603 patients . Tenofovir , Ritonavir boosted atazanavir and ritonavir boosted

Lopinavir were independent predictors of confirmed eGFR <70ml/min indicated chronic renal impairment in HIV positive patients[77] .

Distribution of cases according to CD4 count and its correlation eGFR at the end of study :

In this study , CD4 count at the end of study which is less than 200 were noted in 24 % of patients .Of which 2 patients had < 100 and 21 patients had 100 to 200 CD4 counts. Majority of patients with decline in CD4 count <200 are in less than 60 eGFR category

DART Trial, Longo Ab et al. and other studies have shown that CD4 counts of <200 cells/μL were predictive of impaired renal function and that HIV patients with this severe immune deficiency were more likely to develop CKD, particularly if the viral load was >100,000 copies/mL and were not on HAART.

Relationship between WHO clinical staging and eGFR :

In this present study , majority of HIV patients were in WHO clinical stage T1 (67%) , and 7 % in T2 , 12% in T3 and and 14 % in T4.

In the category of < 60 ml/min eGFR , 71 % of T4 and only 36 % of T1 patients was present, though the frequency of cases was more in T 1

stage . This indicates that as the stage of the disease increases ,there is mild to moderate reduction in eGFR can occur.

However in DART Trial 56% in WHO T3 and 23% WHO T 4. From literature review it was assumed that ,most of the patients with renal dysfunction would be in Stage 4 with AIDS defining illness.

Relationship between Opportunistic infections and e GFR :

In the present study ,there was no correlation between opportunistic infections and eGFR at the end of study .

Among our study population apart from Tenofovir based regimen, female sex , higher age group , high creatinine value , microalbuminuria , CD4 count less than 200 cells /mm^3 and WHO clinical stage 2 or above are the important predictors of renal dysfunction ,and they were having high likelihood of low eGFR at initiation of HAART.

SUMMARY

This study was undertaken to describe the influence of ART drugs on e GFR. The study was conducted in Coimbatore medical college with a study population of 100 patients.

1. The mean age of presentation in our study population was 40.08. There is significant correlation between age and eGFR.
2. In our study 56 % are females, under age group 31- 35. The difference of average in eGFR between male and female is not statistically significant.
3. Mean weight is 48.45 Kg. No significant correlation between weight and decline in eGFR.
4. Mean Creatinine is 1.028. There is significant P value between Creatinine and eGFR. Average levels of Creatinine is significantly higher (1.26) for <60 eGFR category
5. Mean eGFR is 69.28. 20 % of patients with normal baseline eGFR falls into severe decline in eGFR at the end of study after with ART initiation
6. 70% (70 patients) of patients fall under Tenofovir based regimen. Of which 64 % patients falls in eGFR <90 ml/min and in particular 38% falls under eGFR < 60 ml/min which indicates moderate to severe renal dysfunction.

7. Tenofovir based regimen is responsible for most of the decline in renal function with 38% in <60 eGFR category in contrast to only 4% of patients in Zidovudine based regimen comes under < 60ml/min.
8. In our study 47% had albuminuria . Among them , 26 % have significant albuminuria (2+, 3+) and all patients had significant decline in eGFR of < 60 .There is a significant P value between Urine albumin and eGFR .
9. 15% study population had abnormal kidney size and altered echoes in USG KUB and all patients were in eGFR < 60 category .
10. The patients with CD 4 count less than 200 had more fall in GFR compared to other people with increased CD4 values.
11. Most of the patients in our study group falls under WHO Stage 1. As stage of the disease increases, decline in eGFR also increases. In stage T 4 , 71% were in < 60 eGFR category.
12. There is no correlation between opportunistic infection and decline in GFR. This present study indicates that associated opportunistic infections does not influence the decline in renal function . As the duration of study and sample size is less, when compared to other studies , OI"s influence on renal function along with nephrotoxic Antiretroviral drugs cannot be studies exactly.

LIMITATIONS OF THE STUDY

Our study is limited , because comparisons are based on uncalibrated creatinine measurements used for clinical management , and other renal parameters like 24 hour urine protein and renal biopsy was not done , making it impossible to distinguish between kidney disease of different origin or look into systematically for tubular impairment.

Furthermore , eGFR was not directly measured but was estimated using the Cockcroft – Gault formula, and neither this formula nor any other formula has been validated in HIV infected patients. However , creatinine based GFR estimation is preferred better to serum creatinine alone , which have a much lower sensitivity for detecting renal impairment .

CG formula is better than MDRD formula ,because MDRD formula does not contain an explicit factor for weight .In resource limited setting like ours , where patients have severe HIV disease , this has the considerable disadvantage of ignoring substantial weight gain after ART initiation , with increases in muscle mass likely to be responsible for at least some of the increase in serum creatinine .

The study was based at a single academic center and the sample size was small when compared to incidence of HIV cases, and our

experience may differ from other parts of the world where HIV disease is pandemic. Further studies with large sample size are required in India to evaluate and posulate the other predictors of renal dysfunction along with eGFR in HIV patients and the influence of different Antiretroviral drugs for decline in renal function .

CONCLUSION

This study signifies that Tenofovir based regimen is the basis for most of the decline in renal function in patients on ART. Renal dysfunction is highly prevalent in the study population . This highlights the critical and underappreciated need to monitor renal function in HIV positive patients attending ART clinic at CMCH , particularly in this era where Tenofovir is being used in first line ART regimen in majority of patients as recommended by WHO.

So frequent screening of renal function at regular intervals is mandatory in Tenofovir based regimen when compared to other regimens to avoid the further complications in a HIV patient , who is already suffering a incurable dreadful disease .

We also recommend assessment of renal function of HIV infected patients prior to initiation of HAART to guide the choice and dosing of Antiretroviral drugs.

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PROFORMA

Serial No :

Patient information

Name : IP No : Income :

Age ; Sex : ART No: Address:

Occupation :

Diagnosis :

Symptoms

Fever : Yes/No Dysnea : Yes/No

Vomittint : Yes/No Palpitation : Yes /No

Diarrheoa : Yes /No Cough : Yes/No

Pedal Edema : Yes/No Syncope : Yes /No

Facial puffiness : Yes/No Weight loss : Yes / No

Decreases urine output : Yes/No Miscellaneous : Yes /No

Past History :

Diabetes :

Hypertension :

Past drug History or any ART intake :

Chronic renal failure :

Associated illness :

General physical examination

Pulse : Pallor : Emaciation : Pedal edema :

BP : Icterus : Oral thrush : Facial puffiness:

RR : Cyanosis : Clubbing :

Lymphadenopathy:

Temp : Weight (KG):

CVS :

RS :

PA : CNS :

INVESTIGATIONS & DATA s collected :

1) Baseline Urea (Before ART) :

2) Baseline Creatinine (Before ART) :

3) At the end of 10^{th} month Urea :

4) At the end of 10^{th} month Creatinine :

5) Urine Albumin :

6) Ultrasound KUB (Kidney , Bladder, Ureter) : Renomegaly

present /absent

7) Baseline CD 4 count :

8) At the end CD 4 count :

9) Type of regimen started : TLN/ TLE / ZLN /ZLE

10) Stage of the disease :

11) Associated opportunistic infection (OI ‘s)

Throughout the course of study :

12) Miscellaneous :

MASTER CHART

SL.NO	NAME	AGE	SEX	WT	UREA	CREAT	eGFR	UREA	CREAT	eGFR	URINE	USG		CD4	OI'S	STAGE	REGI
1	Puspha	44	F	45	25	0.7	72	22	1	51	Trace	Nor	Q	R	No	T3	A
2	Nagamani	34	F	50	28	1	62.5	40	1.2	52.1	Nil	Nor	Q	R	PT	T1	B
3	Kavitha	34	F	40	25	1	50	20	0.8	62.5	Nil	Nor	P	P	PT	T2	B
4	Raman	33	M	46	22	0.7	97.6	18	1.2	56.9	Trace	Nor	P	R	PT	T3	B
5	Murugeshan	44	M	55	24	1.1	66.6	26	1.2	61.1	Trace	Nor	R	R	No	T1	C
6	Duraisamy	56	M	50	23	1.4	41.6	30	1.8	32.4	3+	R*	R	R	No	T1	A
7	Sokkalingam	51	M	54	25	0.9	74.2	20	0.9	74.2	Trace	Nor	R	R	No	T1	C
8	Sanjay	32	M	46	24	0.9	98.5	29	1.2	57.5	1+	Nor	P	R	PT	T4	D
9	Hussain	35	M	56	33	0.9	90.7	25	0.7	116.6	Nil	Nor	R	Q	Acute GE	T1	C
10	Sarojini	36	F	54	24	0.5	132.6	26	1.2	55.5	Trace	Nor	R	R	No	T1	B
11	Mallika	40	F	58	41	1.1	62.2	28	1.2	57	1+	Nor	R	R	No	T1	A
12	Arputhamani	31	M	50	29	0.8	94.6	28	1.1	94.6	1+	Nor	R	R	No	T1	C
13	Marimuthu	44	M	44	36	0.9	65.2	33	0.9	58.6	Nil	Nor	Q	R	Tb Meningitis	T4	B
14	Rajeswari	49	F	55	30	1	55.8	28	1.2	50.7	Trace	Nor	R	R	No	T3	B
15	Meena	39	F	42	40	0.7	71.5	27	0.5	100.2	Nil	Nor	P	Q	No	T1	C
16	Raja	40	M	56	28	0.8	97.2	30	1	97.2	Nil	Nor	R	R	HZ	T1	C
17	Murugesan	49	M	51	28	0.9	70.2	44	0.8	80	Nil	Nor	R	R	No	T1	A
18	Balanangammal	49	F	49	27	0.7	75.2	28	0.8	65.8	Nil	Nor	R	R	No	T1	B
19	Rangananthan	43	M	45	37	0.9	67.3	27	1.2	50.5	Trace	Nor	Q	R	Tb Pleural effusion	T4	D
20	Kamatchi	33	F	38	20	0.9	43.3	28	0.6	65	Nil	Nor	Q	Q	PT	T3	D
21	Ramasamy	27	M	27	35	0.8	98	35	1.2	60.3	Nil	Nor	R	R	No	T1	A
22	Jancy	33	F	33	36	0.7	77.5	23	1.2	45.2	Trace	Nor	P	R	HZ	T1	A
23	Ramalingam	56	M	48	33	1.2	46.6	35	0.6	93.3	Nil	Nor	Q	Q	No	T1	A
24	Nanjammal	70	F	46	24	1	38	28	1.2	31.6	2+	R*	Q	R	No	T1	A
25	Krishnaveni	40	F	47	29	0.8	69.3	16	0.5	110.9	Nil	Nor	Q	R	Acute GE	T1	C
26	Kalaivani	34	F	50	28	1.1	56.8	30	1.2	52.14	Nil	Nor	R	R	No	T1	C
27	Manikandan	28	M	54	26	0.6	140	28	1.1	76.3	Nil	Nor	R	Q	No	T1	B
28	Kalikutty	35	M	55	30	1	80.2	32	1.4	57.2	Trace	Nor	R	Q	Acute GE	T3	B
29	Poongodi	30	F	40	24	0.8	64.9	25	1.4	37	2+	R*	P	Q	CNS Toxoplasmosis	T4	A
30	Rukmani	42	F	47	15	1	54.3	19	0.6	90.6	Nil	Nor	Q	Q	No	T2	A
31	Baby	40	F	49	24	0.9	64.2	19	0.6	64.2	Nil	Nor	Q	R	No	T1	C
32	Kumar	35	M	56	32	0.9	90.7	32	0.9	102.8	Nil	Nor	Q	R	No	T2	C
33	Sivakolundu	42	M	55	20	0.6	124.7	25	0.8	106.4	Nil	Nor	Q	R	Tb lymphadenitis	T1	C
34	Lakshmi	40	F	48	35	1	56.6	33	0.7	56.6	1+	R*	Q	Q	No	T1	**A**
35	Harisudhan	20	M	35	23	0.6	97.2	37	0.8	72.9	Nil	Nor	Q	Q	No	T1	C
36	Dharmaraj	60	M	51	30	0.4	141	25	0.5	80.9	Nil	Nor	R	R	PT	T1	B
37	Subramaniyan	57	M	54	40	0.4	155.6	30	0.7	51.8	Nil	Nor	R	R	No	T1	B
38	Palaniyammal	35	M	53	28	1	77.2	28	1.2	77.2	Trace	Nor	R	R	No	T1	A
39	Saraswathy	38	F	53	19	0.8	71.9	21	1	57.5	NIl	Nor	R	R	No	T1	B

40	Shanthamani	45	F	45	34	0.8	63	40	1.2	42.05	1+	R*	P	Q	OC+ HIV ppathy	T3	B
41	Moorthy	27	M	56	26	1.1	79.8	24	0.8	109.8	Nil	Nor	R	R	PT	T1	C
42	Bhagawatheswari	30	F	46	28	0.7	85.3	27	0.8	99.5	Nil	Nor	P	R	Tb lymphadenitis	T3	C
43	Subhashini	30	F	48	27	0.7	89	24	0.5	124.6	Nil	Nor	R	R	No	T1	A
44	Krishnasamy	53	M	58	29	1.2	58	31	0.8	87.6	Nil	Nor	R	R	No	T1	C
45	Sagunthan	50	M	55	29	0.7	98.2	20	0.8	85.9	Nil	Nor	R	R	HZ	T1	A
46	Dharmaraj	45	M	50	20	0.7	94.2	18	0.8	82.4	Nil	Nor	R	R	Tb spine	T4	C
47	Nirmala	48	F	46	27	0.9	55.5	23	0.6	83.2	Nil	Nor	Q	R	No	T1	C
48	Manikandan.K	43	M	57	21	1	76.7	22	1.4	54.8	1+	R*	R	R	Tb Pleural effusion	T4	B
49	Shanmugam	45	M	42	35	0.8	69.2	29	1.1	50.3	Trace	Nor	P	R	No	T1	A
50	Vanitha	31	F	43	23	0.7	79.1	24	1	55.3	Trace	Nor	P	R	HZ	T1	A
51	Kavitha	20	F	39	19	0.7	78.9	30	1.2	46.04	2+	R*	R	R	No	T1	B
52	Vairam	50	F	54	23	0.6	95.6	25	1.2	47.8	2+	R*	R	Q	No	T1	B
53	Sivagamisundari	81	F	44	23	0.9	34.5	23	0.6	25.5	Trace	Nor	P	Q	No	T4	B
54	Papa	44	F	52	23	0.5	117	25	0.7	98.2	Nil	Nor	R	R	Acute GE	T1	B
55	Jayalakshmi	48	F	57	28	0.6	103	24	0.5	88.4	Nil	Nor	R	Q	No	T1	B
56	Unnamalai	35	F	40	27	0.7	70.8	31	1.1	99.16	Nil	Nor	P	R	OC	T2	B
57	Sundharambhal	40	F	40	24	1	47.2	26	1.2	39.5	Trace	Nor	R	R	No	T1	A
58	Saroja	40	F	40	24	1	49.5	31	1.4	35.4	Trace	Nor	Q	R	SEBORRHEA	T1	A
59	Murugeshan	27	M	50	25	1	78.4	28	0.8	98	Nil	Nor	R	R	Tb Pleural Effusion	T1	D
60	Dhanapal	48	M	55	29	0.7	103.7	28	1.2	60.4	Trace	Nor	Q	R	PPE	T1	B
61	Mailathal	60	F	47	24	1	44.3	29	1.2	36.9	1+	R*	R	R	No	T1	B
62	Sundaram	60	M	49	28	1.2	45.3	32	1.4	60.4	1+	Nor	Q	Q	PCP	T4	B
63	Babu	50	M	54	40	0.7	96.4	40	1.2	56.2	Trace	Nor	Q	R	No	T1	B
64	Mariappan	45	M	43	24	0.4	141	31	1.3	37.8	2+	R*	P	P	PT+PCP	T4	D
65	Vinothini	21	F	46	24	0.6	107.7	27	0.5	129	Nil	Nor	R	R	OC	T2	C
66	Sampathkumar	43	M	56	24	0.8	94	32	1	75.4	Nil	Nor	R	R	PT	T1	B
67	Vasanthi	30	F	54	27	0.9	77.9	33	1.3	77.9	Nil	Nor	R	R	HZ	T1	A
68	Baskaran	32	M	54	31	0.8	101.2	32	1.4	67.5	Trace	Nor	R	R	No	T1	B
69	Anandhi	40	F	55	24	0.6	108.2	24	0.8	81.1	Nil	Nor	R	R	No	T1	B
70	Chithra	26	F	41	27	0.8	68.9	33	1.5	39.4	1+	Nor	R	R	No	T1	B
71	Sathiyarani	33	F	44	27	0.8	69.4	34	1.3	37	1+	R*	R	R	No	T1	B
72	Eswari	39	F	52	20	0.8	77	24	0.9	69	Trace	Nor	R	R	Acute GE	T1	B
73	Radhamani	35	F	54	25	0.9	74.3	40	1.2	55.7	Trace	Nor	Q	R	PPE	T1	B
74	Palanisamy	34	M	52	25	0.9	85	28	0.6	127.5	Nil	Nor	Q	R	SEBORRHEA	T4	D
75	Saravanan	30	M	56	31	1.5	57	28	0.6	143	Nil	Nor	R	R	PT	T1	C
76	Shanmugapandi	35	M	49	26	0.8	89.3	31	1.2	79	Nil	Nor	Q	R	No	T2	A
77	Sutha	30	F	52	22	0.9	75	32	1.4	56.2	Nil	Nor	Q	Q	HZ	T2	A
78	Manickam	41	M	54	32	0.9	82.5	34	1.3	83	Nil	Nor	Q	R	PPE	T1	A
79	Rajathi	56	F	54	24	0.9	70	33	1.6	43	2+	R*	R	R	Acute GE	T1	A
80	Meenakshi	44	F	46	23	0.9	57.9	27	0.6	87	Nil	Nor	Q	R	No	T1	A

81	Manimegalai	28	F	45	25	0.8	74.3	28	0.8	74	Nil	Nor	R	R	No	T1	B
82	Venkatakrishnan	50	M	53	21	0.5	132	26	1	66	Nil	Nor	R	R	Tb meningitis	T4	B
83	Bharani	20	F	42	20	0.7	107	24	0.5	115	Nil	Nor	R	R	No	T1	A
84	Santhamani	40	F	56	29	1	67	24	0.8	84	Nil	Nor	R	R	PT	T3	D
85	Saravanan	35	M	50	30	0.5	145	31	1.2	73	Nil	Nor	Q	Q	PT	T3	D
86	Vasanthi	53	F	49	27	1.2	42	23	0.7	72	Trace	Nor	R	R	No	T1	C
87	Sumathi	28	F	45	26	0.7	85	29	0.8	119	Nil	Nor	Q	R	No	T1	C
88	Sethulakshmi	48	F	42	30	0.8	57	32	1.3	51	Trace	Nor	P	R	PT+PCP	T3	B
89	Mani	52	M	46	28	0.8	70.2	28	0.9	63	Trace	Nor	Q	R	PT	T3	A
90	Ganesan	35	M	42	21	0.8	76.5	27	1.7	36	1+	Nor	Q	R	No	T1	B
91	Jayanthi	29	F	43	26	0.7	80.4	32	1.4	40	1+	Nor	R	R	PT+PCP	T1	B
92	Vanitha	35	F	47	25	1.2	48.5	27	0.7	84	Nil	Nor	Q	R	No	T1	A
93	Kasthuri	33	F	49	26	0.7	90.2	25	0.6	105	Nil	Nor	R	R	HZ	T1	C
94	Senbagavalli	25	F	40	31	1	54.3	34	1.6	34	2+	R*	P	Q	PT+PCP	T3	B
95	Shanmugam	37	M	55	27	0.8	98.3	31	1.2	66	Nil	Nor	R	R	PT+OC	T1	A
96	Sarathamani	55	F	52	20	0.9	102	28	1	62	Nil	Nor	R	R	No	T1	B
97	Krishna Roa	45	M	46	24	0.9	101	20	0.9	71	Trace	Nor	R	R	No	T1	B
98	Mariammal	24	F	39	26	0.8	67	32	1.5	35.6	2+	Nor	P	Q	CMV RETINITIS	T4	B
99	Petchiammal	55	F	43	22	0.7	62	36	1.8	24	3+	R*	P	Q	CNS ASMOSIS	T4	B
100	Kumari	33	F	47	20	1	60	38	1.8	33	3+	R*	P	Q	HIV Myelopathy	T4	B

MASTER CHART

B	:	Baseline value
E	:	value at the end of 10 months
M	:	Male
F	:	Female
P	:	CD4 count <100
Q	:	CD4 count 100- 200
R	:	CD4 count > 200
R*	:	Renomegaly/ Contracted kidney
eGFR	:	Estimated glomerular Filtration Rate
ALB	:	Albumin
USG KUB	:	Ultrasound kidney Bladder Ureter
OI's	:	Opportunistic Infections
PT	:	Pulmonary tuberculosis
GE	:	Gastroenteritis
OC	:	Oral /Oesophageal candidiasis
PPE	:	Pruritic Papular eruptions
PCP	:	Pneumocystitis carnii pneumonia
A	:	Regimen TLN (tenofovir,Lamivudine , Nevirapine)
B	:	Regimen TLE (Tenofovir, Lamivudine, Efavirenz)
C	:	Regimen ZLN (Zidovudine, Lamivudine,Nevirapine)
D	:	Regimen ZLE (Zidovudine , Lamivudine , Efavirenz)

CONSENT FORM

Yourself Mr./Mrs./Ms. …… are being asked to be a participant in the research study titled

"Estimated Glomerular Filtration Rate As A Predictor Of Renal Dysfunction Among Adult HIV Patients On HAART" in CMC hospital, Coimbatore , conducted by DR.GAYATHRI., Post Graduate Student, Department of General Medicine, Coimbatore Medical College. You are eligible after looking into the inclusion criteria .You can ask any question which you may have before agreeing to participate.

Research Being Done :

Estimated Glomerular Filtration Rate As A Predictor Of Renal Dysfunction Among HIV Patients On HAART .

Purpose of Research :

1. To study the Renal Changes in Adult HIV Patients following first line HAART initiation using eGFR.
2. To study the Renal changes and decline in eGFR with respect to the different HAART regimens after the HAART initiation by using Cockcroft – Gault formula

Decline from Participation :

You have the option to decline from participation in the study existing protocol for your condition.

Privacy and Confidentiality :

Privacy of individuals will be respected and any information about you or provided by you during the study will be kept strictly confidential.

Authorization to publish Results :

Results of the study may be published for scientific purposes and/or presented to scientific groups, however you will not be identified.

Statement of Consent :

I volunteer and consent to participate in this study. I have read the consent or it has been read to me . The study has been fully explained to me, and I may questions at any time.

…… ……

Signature/Left thumb impression Date

(volunteer)

…… ……

Signature of witness Date

xg;g[jy; gotk;

bgah; : taJ :

ghypdk; :

Kfthp:

muR nfhit kUj;Jtf; fy;Y}hapy; bghJ kUj;Jtj; Jiwapy; gl;l gapYk; khztp mth;fs; nkw;bfhs;Sk; **“vr;/l/tp nehahspfspy; v/Mh;/o khj;jpiu cl;bfhs;gth;fspy; rpWePuf ghjpg;gpid Kd;Tl;ona mwpa cjt[k; $p/vg;/Mh;”** Fwpj;j Ma;tpy; bra;Kiw kw;Wk; midj;J tptu';fisa[k; nfl;Lf; bfhz;L vdJ re;njf';fis bjspt[g;gLj;jpf; bfhz;nld; vd;gij bjhptpj;Jf;bfhs;fpnwd;/

ehd; ,e;j Ma;tpy; KG rk;kjj;JlDk;. Ra rpe;jida[lDk; fye;J bfhs;s rk;kjpf;fpnwd;/

,e;j Ma;tpy; vd;Dila midj;J tpgu';fs; ghJfhf;fg;gLtJld; ,jd; Kot[fs; Ma;tpjHpy; btspaplg;gLtjpy; Ml;nrgid ,y;iy vd;gij bjhptpj;Jf; bfhs;fpnwd;/ ve;j neuj;jpYk; ,e;j Ma;tpypUe;J ehd; tpyfpf; bfhs;s vdf;F chpik cz;L vd;gija[k; mwpntd;/

,lk; : ifbahg;gk; - nuif

ehs; :